Defendants' Claim Construction Presentation

Seagen Inc. v. Daiichi Sankyo Company, Limited

Case No. 2:20-cv-00337

Honorable Chief District Judge Rodney Gilstrap

August 27, 2021

Disputed Claim Terms

Drug Moiety

Spacer Unit and Self-Immolative Spacer

Drug-Linker Issues

Intracellularly Cleaved

Disputed Claim Terms

Drug Moiety

Spacer Unit and Self-Immolative Spacer

Drug-Linker Issues

Intracellularly Cleaved

Options Presented in This *Markman* Dispute

Drug Moiety: "D is a drug moiety"

Defendants' Construction	Seagen's Construction
"a drug of the dolastatin/auristatin-type having a nitrogen atom that can form a bond with the Spacer unit when y=1 or 2, or with the C-terminal carboxyl group of an Amino Acid unit when y=0" *See, e.g.*, '039 patent, 71:18-37.	Plain meaning/no construction is necessary. Alternatively, "D is a drug portion"

Seagen's Declarant Agrees the Claim Term "Drug Moiety" Is Defined in Section 9.4

- Seagen disregards the Patentee's lexicography and relies instead on extrinsic evidence from Pamela Trail, Ph.D. (a former Seagen employee and current Seagen stockholder)

- But Dr. Trail's deposition testimony confirms the Patentee's lexicography:

  Q. Where in the '039 patent did you find a definition for the term "drug moiety"?

  A. As we discussed, in 9.4.

  Trail Tr. 119:5-7.

- Seagen seeks to erase this admission via "[c]larification" in an erratum, which still concedes that Section 9.4 defines "drug moiety":

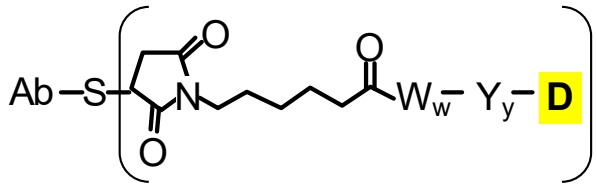
  Q. Where in the '039 patent did you find a definition for the term "drug moiety"?

  A. As we discussed, in 9.4*, column 71, lines 36 through 38*.

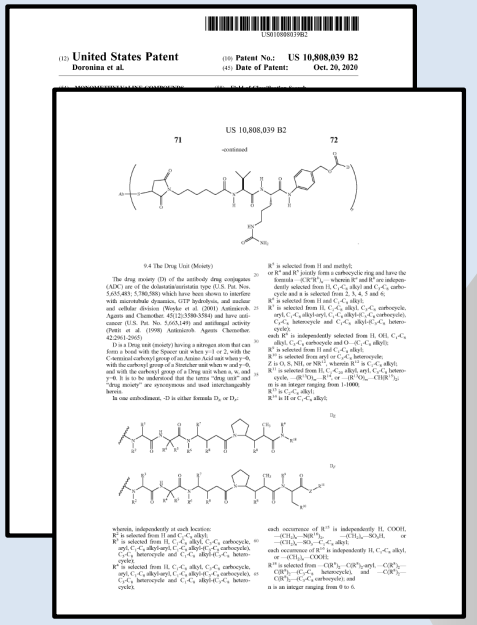
  Trail Tr., Errata Sheet
  (italicized text added by Seagen's erratum).

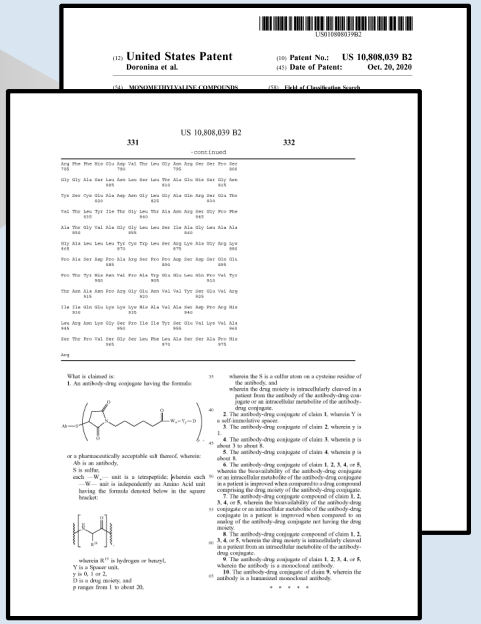
Patentee Used Lexicography to Define "Drug Moiety"

1. An antibody-drug conjugate having the formula:



. . . wherein . . . D is a drug moiety . . . .





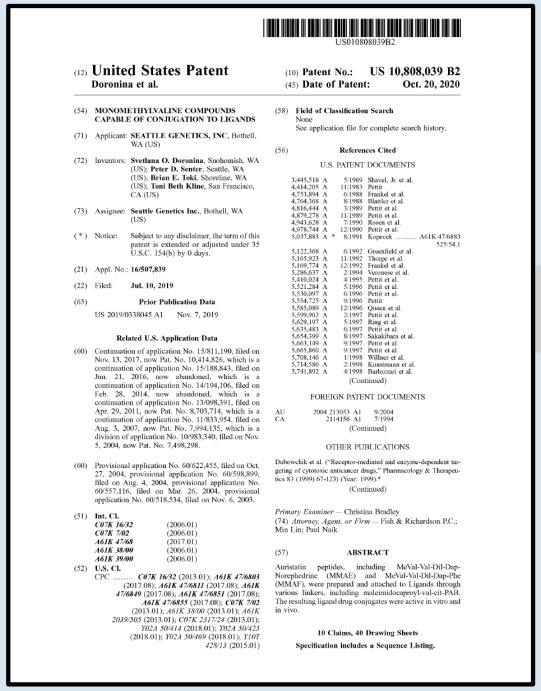
9.4 The Drug Unit (Moiety)

The drug moiety (D) of the antibody drug conjugates (ADC) ***are*** of the dolastatin/auristatin type . . . .

D ***is*** a Drug unit (moiety) having a nitrogen atom that can form a bond with the Spacer unit when y=1 or 2, with the C-terminal carboxyl group of an Amino Acid unit when y=0 . . . . It is to be understood that the terms "drug unit" and "drug moiety" are synonymous and used interchangeably herein.

See, e.g., '039 patent, 71:18-37 (emphases added), Claim 1.

’039 Patent: Title



US010808039B2

(12) **United States Patent**
Doronina et al.

(10) **Patent No.: US 10,808,039 B2**
(45) **Date of Patent: Oct. 20, 2020**

(54) **MONOMETHYLVALINE COMPOUNDS CAPABLE OF CONJUGATION TO LIGANDS**

(71) Applicant: **SEATTLE GENETICS, INC**, Bothell, WA (US)

(72) Inventors: **Svetlana O. Doronina**, Snohomish, WA (US); **Peter D. Senter**, Seattle, WA (US); **Brian E. Toki**, Shoreline, WA (US); **Toni Beth Kline**, San Francisco, CA (US)

(73) Assignee: **Seattle Genetics Inc.**, Bothell, WA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/507,839**

(22) Filed: **Jul. 10, 2019**

(65) **Prior Publication Data**

US 2019/0338045 A1 Nov. 7, 2019

Related U.S. Application Data

(60) Continuation of application No. 15/811,190, filed on Nov. 13, 2017, now Pat. No. 10,414,826, which is a continuation of application No. 15/188,843, filed on Jun. 21, 2016, now abandoned, which is a continuation of application No. 14/194,106, filed on Feb. 28, 2014, now abandoned, which is a continuation of application No. 13/098,391, filed on Apr. 29, 2011, now Pat. No. 8,703,714, which is a continuation of application No. 11/833,954, filed on Aug. 3, 2007, now Pat. No. 7,994,135, which is a division of application No. 10/983,340, filed on Nov. 5, 2004, now Pat. No. 7,498,298.

(60) Provisional application No. 60/622,455, filed on Oct. 27, 2004, provisional application No. 60/598,899, filed on Aug. 4, 2004, provisional application No. 60/557,116, filed on Mar. 26, 2004, provisional application No. 60/518,534, filed on Nov. 6, 2003.

(51) **Int. Cl.**
C07K 16/32 (2006.01)
C07K 7/02 (2006.01)
A61K 47/68 (2017.01)
A61K 38/00 (2006.01)
A61K 39/00 (2006.01)

(52) **U.S. Cl.**
CPC ***C07K 16/32*** (2013.01); ***A61K 47/6803*** (2017.08); ***A61K 47/6811*** (2017.08); ***A61K 47/6849*** (2017.08); ***A61K 47/6851*** (2017.08); ***A61K 47/6855*** (2017.08); ***C07K 7/02*** (2013.01); *A61K 38/00* (2013.01); *A61K 2039/505* (2013.01); *C07K 2317/24* (2013.01); *Y02A 50/414* (2018.01); *Y02A 50/423* (2018.01); *Y02A 50/469* (2018.01); *Y10T 428/13* (2015.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

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3,445,518 A 5/1969 Shovel, Jr. et al.
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4,764,368 A 8/1988 Blattler et al.
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4,943,628 A 7/1990 Rosen et al.
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5,037,883 A * 8/1991 Kopecek A61K 47/6883 525/54.1
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5,286,637 A 2/1994 Vercuese et al.
5,410,024 A 4/1995 Petrit et al.
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(Continued)

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Dubowchik et al. ("Receptor-mediated and enzyme-dependent targeting of cytotoxic anticancer drugs," Pharmacology & Therapeutics 83 (1999) 67-123) (Year: 1999).*
(Continued)

Primary Examiner — Christina Bradley
(74) *Attorney, Agent, or Firm* — Fish & Richardson P.C.; Min Lin; Paul Naik

(57) **ABSTRACT**

Auristatin peptides, including MeVal-Val-Dil-Dap-Norephedrine (MMAE) and MeVal-Val-Dil-Dap-Phe (MMAF), were prepared and attached to Ligands through various linkers, including maleimidocaproyl-val-cit-PAB. The resulting ligand-drug conjugates were active in vitro and in vivo.

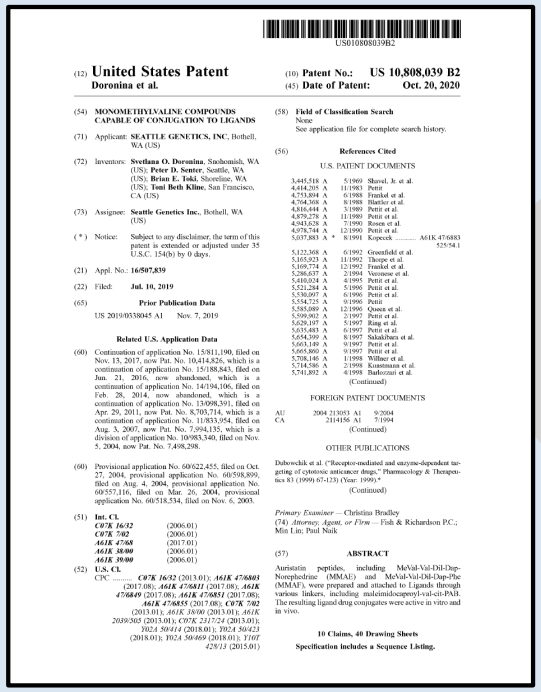
10 Claims, 40 Drawing Sheets
Specification includes a Sequence Listing.

Title: Monomethylvaline Compounds Capable of Conjugation to Ligands

- “Monomethylvaline compounds” are dolastatin/auristatin-type drugs

See, e.g., ’039 patent, (54); Trail Tr. 50:2-15.

’039 Patent: Abstract



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10 Claims, 40 Drawing Sheets
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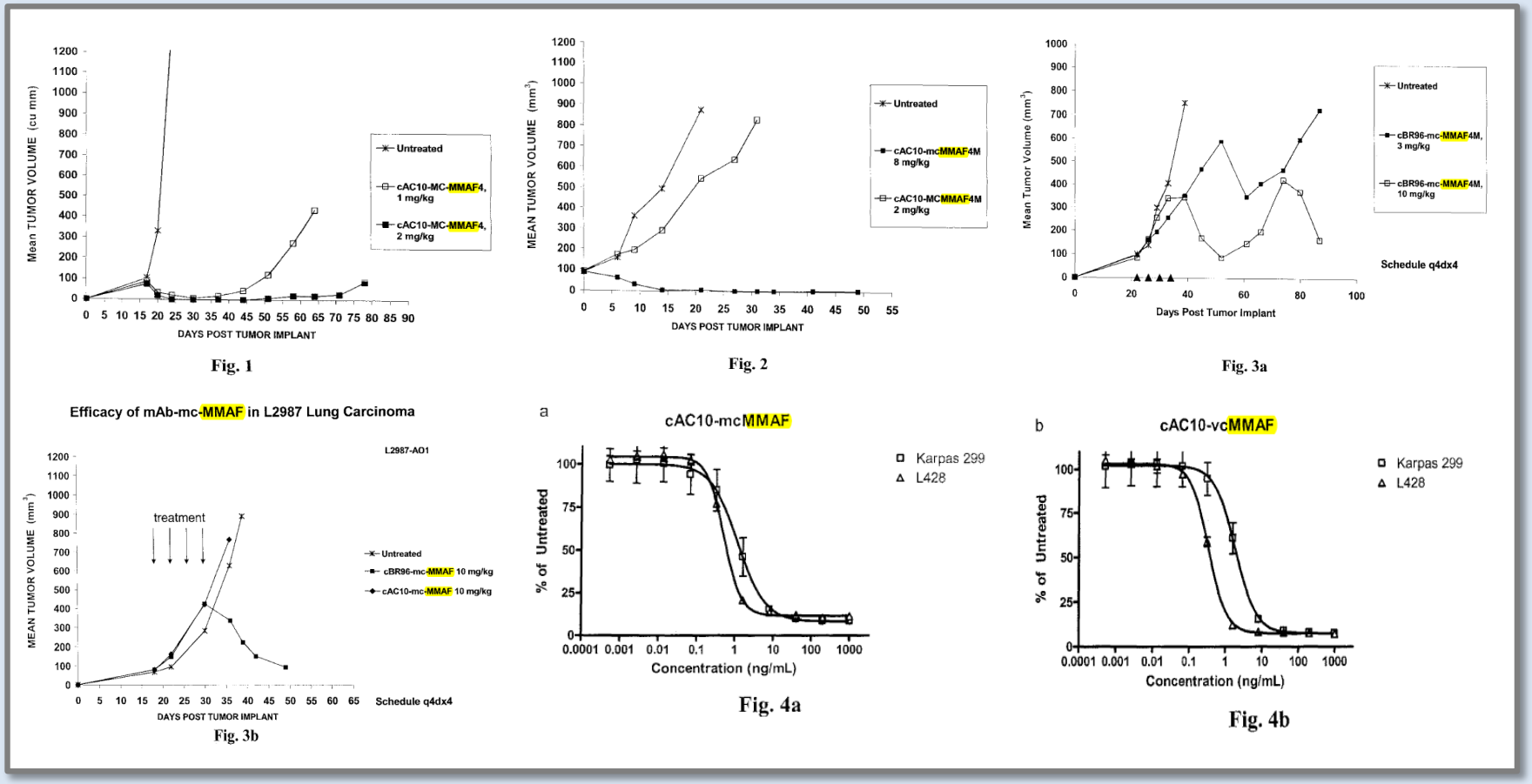
ABSTRACT

Auristatin peptides, including MeVal-Val-Dil-DapNorephedrine (MMAE) and MeVal-Val-Dil-Dap-Phe (MMAF), were prepared and attached to Ligands through various linkers, including maleimidocaproyl-val-cit-PAB. The resulting ligand drug conjugates were active in vitro and in vivo.

- The Abstract refers only to dolastatin/auristatin-type drugs and their use in ligand-drug conjugates

See, e.g., ’039 patent, (57); Trail Tr. 51:13-52:17, 53:2-10.

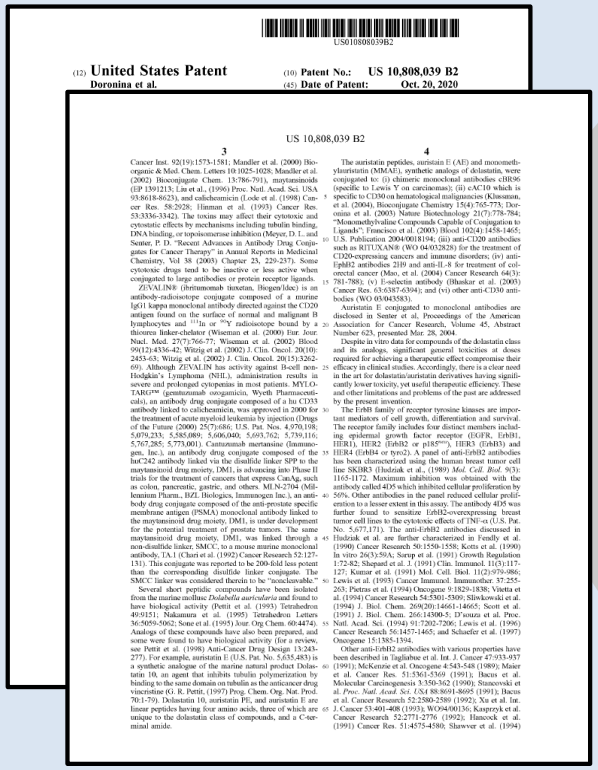
'039 Patent: 40 Sheets of Figures



- Over 40 sheets of figures, every exemplified ADC has a dolastatin/auristatin-type drug moiety

See, e.g., '039 patent, Figs. 1-19, 25-27, 37-39; Trail Tr. 54:2-6.

’039 Patent: Background of the Invention



US10808039B2

(12) **United States Patent**
Doronina et al.

(10) **Patent No.: US 10,808,039 B2**
(45) **Date of Patent: Oct. 20, 2020**

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Cancer Inst. 92(19):1573-1581; Mandler et al. (2000) Bioorganic & Med. Chem. Letters 10:1025-1028; Mandler et al. (2002) Bioconjugate Chem. 13:786-791), maytansinoids (EP 1391213; Liu et al., (1996) Proc. Natl. Acad. Sci. USA 93:8618-8623), and calicheamicin (Lode et al. (1998) Cancer Res. 58:2928; Hinman et al. (1993) Cancer Res. 53:3336-3342). The toxins may affect their cytotoxic and cytostatic effects by mechanisms including tubulin binding, DNA binding, or topoisomerase inhibition (Meyer, D. L. and Senter, P. D. "Recent Advances in Antibody Drug Conjugates for Cancer Therapy" in Annual Reports in Medicinal Chemistry, Vol 38 (2003) Chapter 23, 229-237). Some cytotoxic drugs tend to be inactive or less active when conjugated to large antibodies or protein receptor ligands.

ZEVALIN® (ibritumomab tiuxetan, Biogen/Idec) is an antibody-radioisotope conjugate composed of a murine IgG1 kappa monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes and ^{111}In or ^{90}Y radioisotope bound by a thiourea linker-chelator (Wiseman et al. (2000) Eur. Jour. Nucl. Med. 27(7):766-77; Wiseman et al. (2002) Blood 99(12):4336-42; Witzig et al. (2002) J. Clin. Oncol. 20(10):2453-63; Witzig et al. (2002) J. Clin. Oncol. 20(15):3262-69). Although ZEVALIN has activity against B-cell non-Hodgkin's Lymphoma (NHL), administration results in severe and prolonged cytopenias in most patients. MYLOTARG™ (gemtuzumab ozogamicin, Wyeth Pharmaceuticals), an antibody drug conjugate composed of a hu CD33 antibody linked to calicheamicin, was approved in 2000 for the treatment of acute myeloid leukemia by injection (Drugs of the Future (2000) 25(7):686; U.S. Pat. Nos. 4,970,198; 5,079,233; 5,585,089; 5,606,040; 5,693,762; 5,739,116; 5,767,285; 5,773,001). Cantuzumab mertansine (Immunogen, Inc.), an antibody drug conjugate composed of the huC242 antibody linked via the disulfide linker SPP to the maytansinoid drug moiety, DM1, is advancing into Phase II trials for the treatment of cancers that express CanAg, such as colon, pancreatic, gastric, and others. MLN-2704 (Millennium Pharm., BZL Biologics, Immunogen Inc.), an antibody drug conjugate composed of the anti-prostate specific membrane antigen (PSMA) monoclonal antibody linked to the maytansinoid drug moiety, DM1, is under development for the potential treatment of prostate tumors. The same maytansinoid drug moiety, DM1, was linked through a non-disulfide linker, SMCC, to a mouse murine monoclonal antibody, TA.1 (Chari et al. (1992) Cancer Research 52:127-131). This conjugate was reported to be 200-fold less potent than the corresponding disulfide linker conjugate. The SMCC linker was considered therein to be "nonCleavable."

Several short peptidic compounds have been isolated from the marine mollusc *Dolabella auricularia* and found to have biological activity (Pettit et al. (1993) Tetrahedron 49:9151; Nakamura et al. (1995) Tetrahedron Letters 36:5059-5062; Sone et al. (1995) Jour. Org. Chem. 60:4474). Analogs of these compounds have also been prepared, and some were found to have biological activity (for a review, see Pettit et al. (1998) Anti-Cancer Drug Design 13:243-277). For example, auristatin E (U.S. Pat. No. 5,635,483) is a synthetic analogue of the marine natural product Dolastatin 10, an agent that inhibits tubulin polymerization by binding to the same domain on tubulin as the anticancer drug vincristine (G. R. Pettit, (1997) Prog. Chem. Org. Nat. Prod. 70:1-79). Dolastatin 10, auristatin PE, and auristatin E are linear peptides having four amino acids, three of which are unique to the dolastatin class of compounds, and a C-terminal amide.

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The auristatin peptides, auristatin E (AE) and monomethylauristatin (MMAE), synthetic analogs of dolastatin, were conjugated to: (i) chimeric monoclonal antibodies cBR96 (specific to Lewis Y on carcinomas); (ii) cAC10 which is specific to CD30 on hematological malignancies (Klussman, et al. (2004), Bioconjugate Chemistry 15(4):765-773; Doronina et al. (2003) Nature Biotechnology 21(7):778-784; "Monomethylvaline Compounds Capable of Conjugation to Ligands"; Francisco et al. (2003) Blood 102(4):1458-1465; U.S. Publication 2004/0018194; (iii) anti-CD20 antibodies such as RITUXAN® (WO 04/032828) for the treatment of CD20-expressing cancers and immune disorders; (iv) anti-EphB2 antibodies 2H9 and anti-E-8 for treatment of colorectal cancer (Mao, et al. (2004) Cancer Research 64(3):781-788); (v) E-selectin antibody (Bhaskar et al. (2003) Cancer Res. 63:6387-6394); and (vi) other anti-CD30 antibodies (WO 03/043583).

Auristatin E conjugated to monoclonal antibodies are disclosed in Senter et al, Proceedings of the American Association for Cancer Research, Volume 45, Abstract Number 623, presented Mar. 28, 2004.

Despite in vitro data for compounds of the dolastatin class and its analogs, significant general toxicities at doses required for achieving a therapeutic effect compromise their efficacy in clinical studies. Accordingly, there is a clear need in the art for dolastatin/auristatin derivatives having significantly lower toxicity, yet useful therapeutic efficiency. These and other limitations and problems of the past are addressed by the present invention.

The ErbB family of receptor tyrosine kinases are important mediators of cell growth, differentiation and survival. The receptor family includes four distinct members including epidermal growth factor receptor (EGFR, ErbB1, HER1), HER2 (ErbB2 or p185^{neu}), HER3 (ErbB3) and HER4 (ErbB4 or tyro2). A panel of anti-ErbB2 antibodies has been characterized using the human breast tumor cell line SKBR3 (Hudziak et al., (1989) *Mol. Cell. Biol.* 9(3):1165-1172. Maximum inhibition was obtained with the antibody called 4D5 which inhibited cellular proliferation by 50%. Other antibodies in the panel reduced cellular proliferation to a lesser extent in this assay. The antibody 4D5 was further found to sensitize ErbB2-overexpressing breast tumor cell lines to the cytotoxic effects of TNF-α (U.S. Pat. No. 5,677,171). The anti-ErbB2 antibodies discussed in Hudziak et al. are further characterized in Fendly et al. (1990) Cancer Research 50:1550-1558; Kotts et al. (1990) In vitro 26(3):59A; Sarup et al. (1991) Growth Regulation 1:72-82; Shepard et al. J. (1991) Clin. Immunol. 11(3):117-127; Kumar et al. (1991) Mol. Cell. Biol. 11(2):979-986; Lewis et al. (1993) Cancer Immunol. Immunother. 37:255-263; Pietras et al. (1994) Oncogene 9:1829-1838; Vitetta et al. (1994) Cancer Research 54:5301-5309; Sliwkowski et al. (1994) J. Biol. Chem. 269(20):14661-14665; Scott et al. (1991) J. Biol. Chem. 266:14300-5; D'souza et al. Proc. Natl. Acad. Sci. (1994) 91:7202-7206; Lewis et al. (1996) Cancer Research 56:1457-1465; and Schaefer et al. (1997) Oncogene 15:1385-1394.

Other anti-ErbB2 antibodies with various properties have been described in Tagliabue et al. Int. J. Cancer 47:933-937 (1991); McKenzie et al. Oncogene 4:543-548 (1989); Maier et al. Cancer Res. 51:5361-5369 (1991); Bacus et al. Molecular Carcinogenesis 3:350-362 (1990); Stancovski et al. *Proc. Natl. Acad. Sci. USA* 88:8691-8695 (1991); Bacus et al. Cancer Research 52:2580-2589 (1992); Xu et al. Int. J. Cancer 53:401-408 (1993); WO94/00136; Kasprzyk et al. Cancer Research 52:2771-2776 (1992); Hancock et al. (1991) Cancer Res. 51:4575-4580; Shawver et al. (1994)

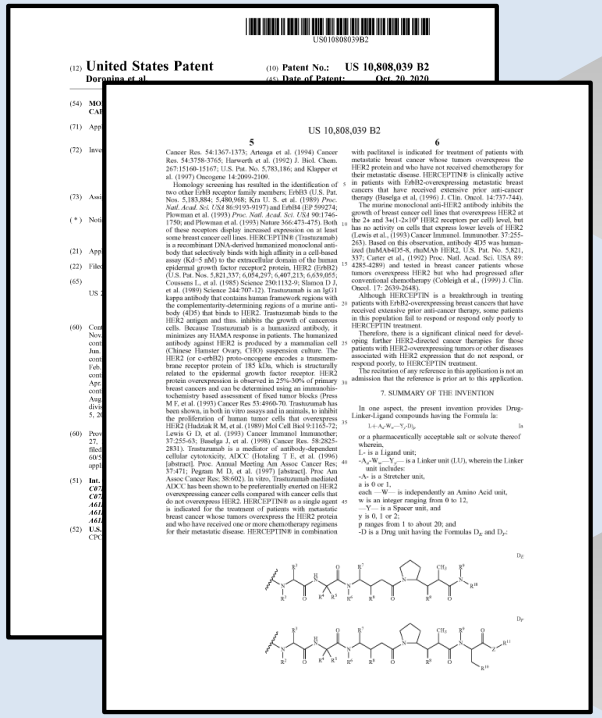
Despite in vitro data for compounds of the dolastatin class and its analogs, significant general toxicities at doses required for achieving a therapeutic effect compromise their efficacy in clinical studies. Accordingly, there is a clear need in the art for dolastatin/auristatin derivatives having significantly lower toxicity, yet useful therapeutic efficiency. These and other limitations and problems of the past are addressed by the present invention.

- The patent purports to fill “a clear need in the art for dolastatin/ auristatin derivatives”

See, e.g., ’039 patent, 4:22-29; Trail Tr. 69:7-70:18.

’039 Patent: Summary of the Invention

- The drug unit (moiety) have formulas based on auristatins MMAE and MMAF: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(12) United States Patent

US 10,808,039 B2

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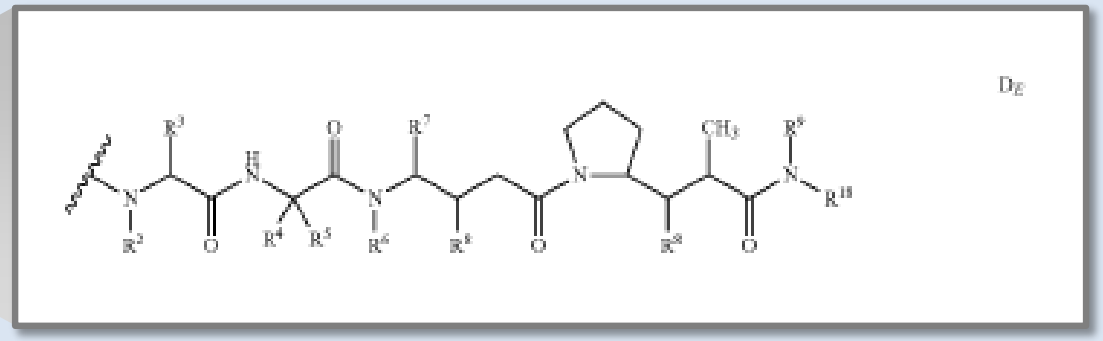
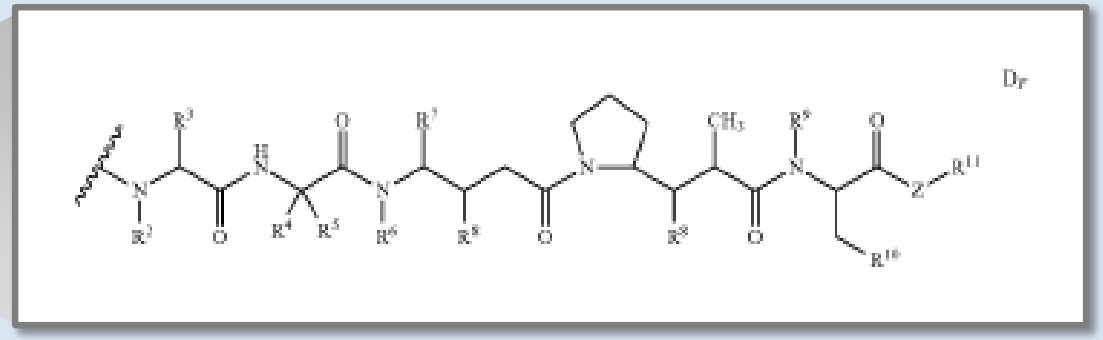
7. SUMMARY OF THE INVENTION

Formula D_E

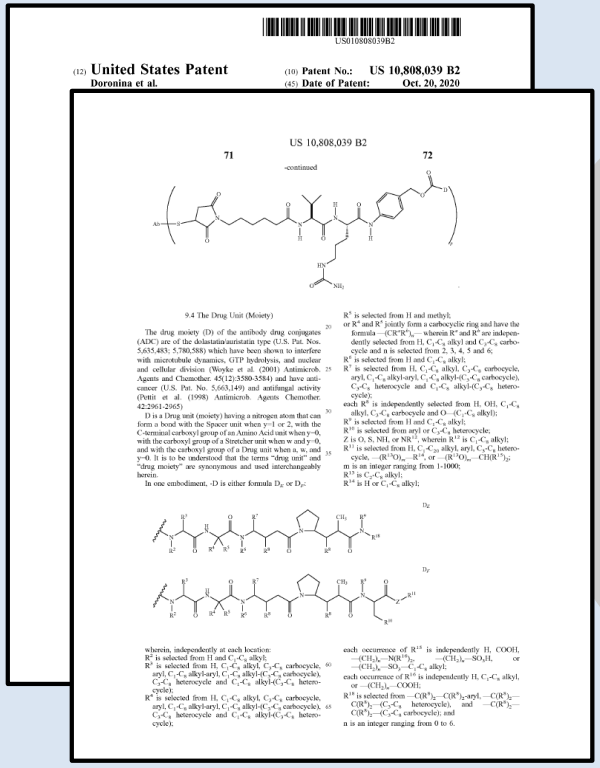


Formula D_F



See, e.g., ’039 patent, 6:31-7:42, 11:5-13:63, 15:42-18:17; *see also, e.g. id.* at 44:55-60:26; Trail Tr. 72:10-25.

’039 Patent: Section 9.4



US10808039B2

(12) **United States Patent**
Doronina et al.

(10) **Patent No.: US 10,808,039 B2**
(45) **Date of Patent: Oct. 20, 2020**

US 10,808,039 B2

71 72

-continued

9.4 The Drug Unit (Moiety)

The drug moiety (D) of the antibody drug conjugates (ADC) are of the dolastatin/auristatin type (U.S. Pat. Nos. 5,635,483; 5,780,588) which have been shown to interfere with microtubule dynamics, GTP hydrolysis, and nuclear and cellular division (Woyke et al. (2001) Antimicrob. Agents and Chemother. 45(12):3580-3584) and have anti-cancer (U.S. Pat. No. 5,663,149) and antifungal activity (Pettit et al. (1998) Antimicrob. Agents Chemother. 42:2961-2965)

D is a Drug unit (moiety) having a nitrogen atom that can form a bond with the Spacer unit when y=1 or 2, with the C-terminal carboxyl group of an Amino Acid unit when y=0, with the carboxyl group of a Stretcher unit when w and y=0, and with the carboxyl group of a Drug unit when u, w, and y=0. It is to be understood that the terms "drug unit" and "drug moiety" are synonymous and used interchangeably herein.

In one embodiment, -D is either formula D_E or D_F:

wherein, independently at each location:
R^2 is selected from H and C_1-C_8 alkyl;
R^3 is selected from H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle and C_1-C_8 alkyl-(C_3-C_8 heterocycle);
R^4 is selected from H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle and C_1-C_8 alkyl-(C_3-C_8 heterocycle);

R^5 is selected from H and methyl;
or R^4 and R^5 jointly form a carbocyclic ring and have the formula $-(CR^aR^b)_n-$ wherein R^a and R^b are independently selected from H, C_1-C_8 alkyl and C_3-C_8 carbocycle and n is selected from 2, 3, 4, 5 and 6;
R^6 is selected from H and C_1-C_8 alkyl;
R^7 is selected from H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle and C_1-C_8 alkyl-(C_3-C_8 heterocycle);
each R^8 is independently selected from H, OH, C_1-C_8 alkyl, C_3-C_8 carbocycle and O—(C_1-C_8 alkyl);
R^9 is selected from H and C_1-C_8 alkyl;
R^{10} is selected from aryl or C_3-C_8 heterocycle;
Z is O, S, NH, or NR^{12}, wherein R^{12} is C_1-C_8 alkyl;
R^{11} is selected from H, C_1-C_{20} alkyl, aryl, C_3-C_8 heterocycle, $—(R^{13}O)_m—R^{14}$, or $—(R^{13}O)_m—CH(R^{15})_2$;
m is an integer ranging from 1-1000;
R^{13} is C_2-C_8 alkyl;
R^{14} is H or C_1-C_8 alkyl;
each occurrence of R^{15} is independently H, COOH, $—(CH_2)_n—N(R^{16})_2$, $—(CH_2)_n—SO_3H$, or $—(CH_2)_n—SO_3—C_1$-C_8 alkyl;
each occurrence of R^{16} is independently H, C_1-C_8 alkyl, or $—(CH_2)_n—COOH$;
R^{18} is selected from $—C(R^8)_2—C(R^8)_2$-aryl, $—C(R^8)_2—C(R^8)_2—(C_3$-C_8 heterocycle), and $—C(R^8)_2—C(R^8)_2—(C_3$-C_8 carbocycle); and
n is an integer ranging from 0 to 6.

9.4 The Drug Unit (Moiety)

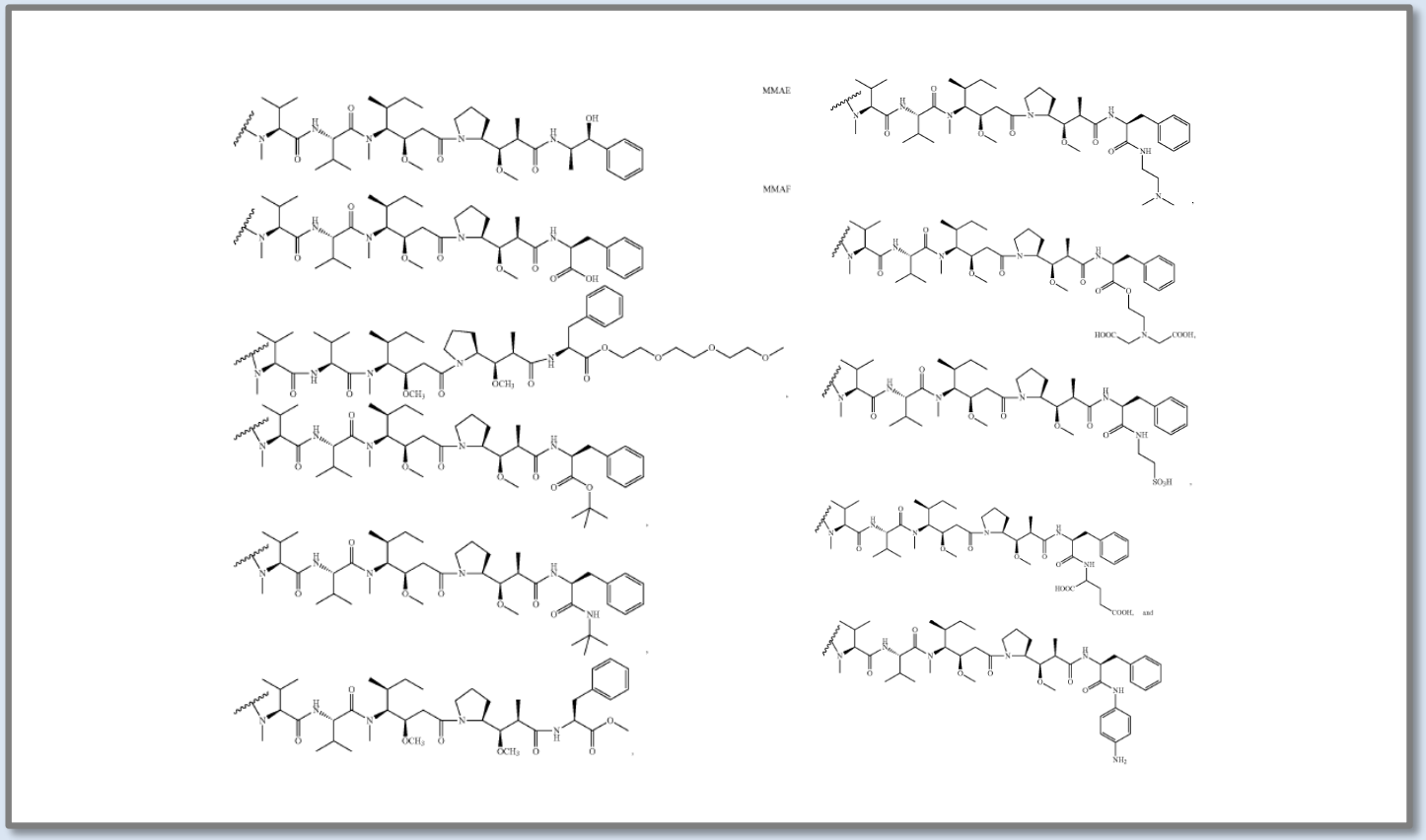
The drug moiety (D) of the antibody drug conjugates (ADC) are of the dolastatin/auristatin type . . . .

D is a Drug unit (moiety) having a nitrogen atom that can form a bond with the Spacer unit when y=1 or 2, with the C-terminal carboxyl group of an Amino Acid unit when y=0 . . . . It is to be understood that the terms “drug unit” and “drug moiety” are synonymous and used interchangeably herein.

See, e.g., ’039 patent, 71:18-37.

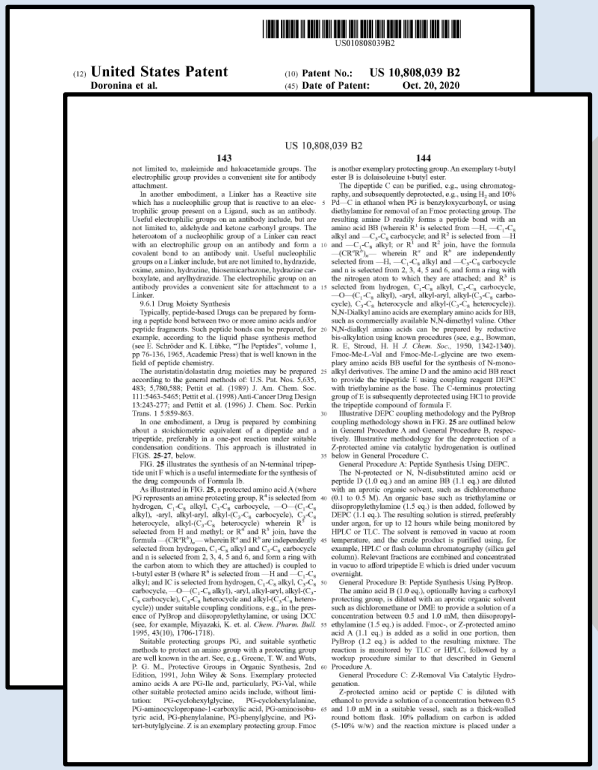
’039 Patent: Section 9.4 Illustrated Drug Moieties

- All illustrated drugs moieties are of the dolastatin/auristatin type:



See, e.g., ’039 patent, 74:10-77:16;
Trail Tr. 72:14-25, 82:6-13, 197:4-9.

’039 Patent: Section 9.6.1 Drug Moiety Synthesis



US010808039B2

(12) **United States Patent**
Doronina et al.

(10) **Patent No.: US 10,808,039 B2**
(45) **Date of Patent: Oct. 20, 2020**

US 10,808,039 B2

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not limited to, maleimide and haloacetamide groups. The electrophilic group provides a convenient site for antibody attachment.

In another embodiment, a Linker has a Reactive site which has a nucleophilic group that is reactive to an electrophilic group present on a Ligand, such as an antibody. Useful electrophilic groups on an antibody include, but are not limited to, aldehyde and ketone carbonyl groups. The heteroatom of a nucleophilic group of a Linker can react with an electrophilic group on an antibody and form a covalent bond to an antibody unit. Useful nucleophilic groups on a Linker include, but are not limited to, hydrazide, oxime, amino, hydrazine, thiosemicarbazone, hydrazine carboxylate, and arylhydrazide. The electrophilic group on an antibody provides a convenient site for attachment to a Linker.

9.6.1 Drug Moiety Synthesis

Typically, peptide-based Drugs can be prepared by forming a peptide bond between two or more amino acids and/or peptide fragments. Such peptide bonds can be prepared, for example, according to the liquid phase synthesis method (see E. Schröder and K. Lübke, "The Peptides", volume 1, pp 76-136, 1965, Academic Press) that is well known in the field of peptide chemistry.

The auristatin/dolastatin drug moieties may be prepared according to the general methods of: U.S. Pat. Nos. 5,635,483; 5,780,588; Pettit et al. (1989) J. Am. Chem. Soc. 111:5463-5465; Pettit et al. (1998) Anti-Cancer Drug Design 13:243-277; and Pettit et al. (1996) J. Chem. Soc. Perkin Trans. 1 5:859-863.

In one embodiment, a Drug is prepared by combining about a stoichiometric equivalent of a dipeptide and a tripeptide, preferably in a one-pot reaction under suitable condensation conditions. This approach is illustrated in FIGS. **25-27**, below.

FIG. **25** illustrates the synthesis of an N-terminal tripeptide unit F which is a useful intermediate for the synthesis of the drug compounds of Formula Ib.

As illustrated in FIG. **25**, a protected amino acid A (where PG represents an amine protecting group, R^4 is selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 carbocycle, —O—(C_1-C_8 alkyl), -aryl, alkyl-aryl, alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle, alkyl-(C_3-C_8 heterocycle) wherein R^5 is selected from H and methyl; or R^4 and R^5 join, have the formula —(CR^6R^7)$_n$— wherein R^6 and R^7 are independently selected from hydrogen, C_1-C_8 alkyl and C_3-C_8 carbocycle and n is selected from 2, 3, 4, 5 and 6, and form a ring with the carbon atom to which they are attached) is coupled to t-butyl ester B (where R^3 is selected from —H and —C_1-C_8 alkyl; and IC is selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 carbocycle, —O—(C_1-C_8 alkyl), -aryl, alkyl-aryl, alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle and alkyl-(C_3-C_8 heterocycle)) under suitable coupling conditions, e.g., in the presence of PyBrop and diisopropylethylamine, or using DCC (see, for example, Miyazaki, K. et al. *Chem. Pharm. Bull.* 1995, 43(10), 1706-1718).

Suitable protecting groups PG, and suitable synthetic methods to protect an amino group with a protecting group are well known in the art. See, e.g., Greene, T. W. and Wuts, P. G. M., Protective Groups in Organic Synthesis, 2nd Edition, 1991, John Wiley & Sons. Exemplary protected amino acids A are PG-Ile and, particularly, PG-Val, while other suitable protected amino acids include, without limitation: PG-cyclohexylglycine, PG-cyclohexylalanine, PG-aminocyclopropane-1-carboxylic acid, PG-aminoisobutyric acid, PG-phenylalanine, PG-phenylglycine, and PG-tert-butylglycine. Z is an exemplary protecting group. Fmoc is another exemplary protecting group. An exemplary t-butyl ester B is dolaisoleuine t-butyl ester.

The dipeptide C can be purified, e.g., using chromatography, and subsequently deprotected, e.g., using H_2 and 10% Pd—C in ethanol when PG is benzyloxycarbonyl, or using diethylamine for removal of an Fmoc protecting group. The resulting amine D readily forms a peptide bond with an amino acid BB (wherein R^1 is selected from —H, —C_1-C_8 alkyl and —C_3-C_8 carbocycle; and R^2 is selected from —H and —C_1-C_8 alkyl; or R^1 and R^2 join, have the formula —(CR^6R^7)$_n$— wherein R^6 and R^7 are independently selected from —H, —C_1-C_8 alkyl and —C_3-C_8 carbocycle and n is selected from 2, 3, 4, 5 and 6, and form a ring with the nitrogen atom to which they are attached; and R^3 is selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 carbocycle, —O—(C_1-C_8 alkyl), -aryl, alkyl-aryl, alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle and alkyl-(C_3-C_8 heterocycle)). N,N-Dialkyl amino acids are exemplary amino acids for BB, such as commercially available N,N-dimethyl valine. Other N,N-dialkyl amino acids can be prepared by reductive bis-alkylation using known procedures (see, e.g., Bowman, R. E., Stroud, H. H *J. Chem. Soc.*, 1950, 1342-1340). Fmoc-Me-L-Val and Fmoc-Me-L-glycine are two exemplary amino acids BB useful for the synthesis of N-monoalkyl derivatives. The amine D and the amino acid BB react to provide the tripeptide E using coupling reagent DEPC with triethylamine as the base. The C-terminus protecting group of E is subsequently deprotected using HCl to provide the tripeptide compound of formula F.

Illustrative DEPC coupling methodology and the PyBrop coupling methodology shown in FIG. **25** are outlined below in General Procedure A and General Procedure B, respectively. Illustrative methodology for the deprotection of a Z-protected amine via catalytic hydrogenation is outlined below in General Procedure C.

General Procedure A: Peptide Synthesis Using DEPC:

The N-protected or N, N-disubstituted amino acid or peptide D (1.0 eq.) and an amine BB (1.1 eq.) are diluted with an aprotic organic solvent, such as dichloromethane (0.1 to 0.5 M). An organic base such as triethylamine or diisopropylethylamine (1.5 eq.) is then added, followed by DEPC (1.1 eq.). The resulting solution is stirred, preferably under argon, for up to 12 hours while being monitored by HPLC or TLC. The solvent is removed in vacuo at room temperature, and the crude product is purified using, for example, HPLC or flash column chromatography (silica gel column). Relevant fractions are combined and concentrated in vacuo to afford tripeptide E which is dried under vacuum overnight.

General Procedure B: Peptide Synthesis Using PyBrop.

The amino acid B (1.0 eq.), optionally having a carboxyl protecting group, is diluted with an aprotic organic solvent such as dichloromethane or DMF to provide a solution of a concentration between 0.5 and 1.0 mM, then diisopropylethylamine (1.5 eq.) is added. Fmoc-, or Z-protected amino acid A (1.1 eq.) is added as a solid in one portion, then PyBrop (1.2 eq.) is added to the resulting mixture. The reaction is monitored by TLC or HPLC, followed by a workup procedure similar to that described in General Procedure A.

General Procedure C: Z-Removal Via Catalytic Hydrogenation.

Z-protected amino acid or peptide C is diluted with ethanol to provide a solution of a concentration between 0.5 and 1.0 mM in a suitable vessel, such as a thick-walled round bottom flask. 10% palladium on carbon is added (5-10% w/w) and the reaction mixture is placed under a

9.6.1 Drug Moiety Synthesis

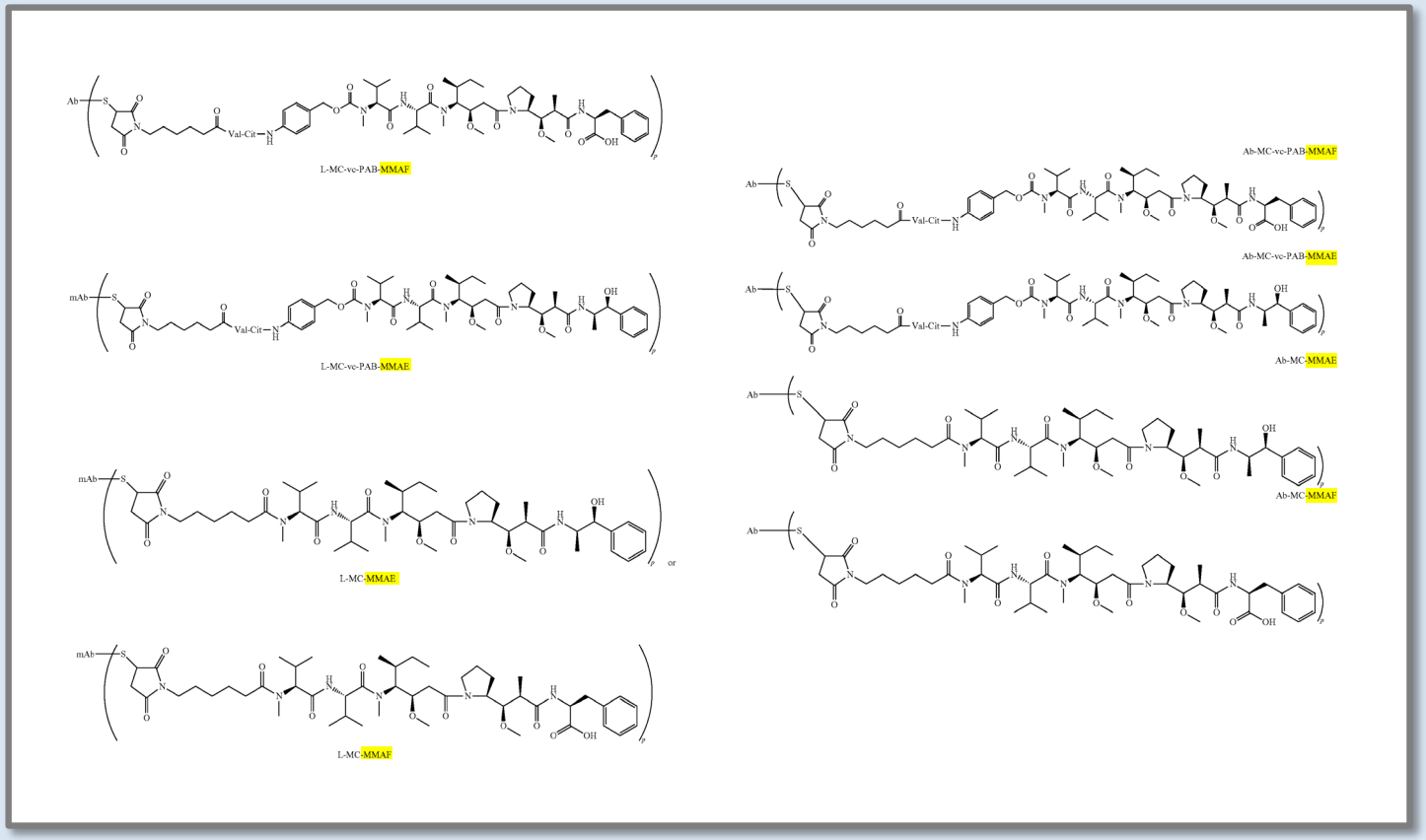
Typically, peptide-based Drugs can be prepared by forming a peptide bond between two or more amino acids and/or peptide fragments. . . .

The auristatin/dolastatin drug moieties may be prepared according to the general methods of: U.S. Pat. Nos. 5,635,483; 5,780,588; Pettit et al. (1989) J. Am. Chem. Soc. 111:5463-5465; Pettit et al. (1998) Anti-Cancer Drug Design 13:243-277; and Pettit et al. (1996) J. Chem. Soc. Perkin Trans. 1 5:859-863.

See, e.g., ’039 patent, 143:17-146:2.

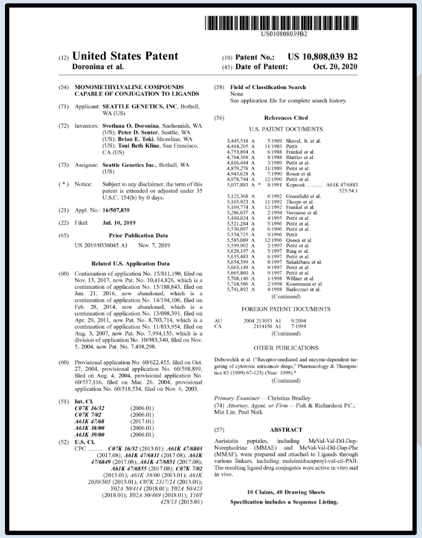
’039 Patent: Illustrated ADCs

- All illustrated ADCs have drug moieties of the dolastatin/auristatin-type:



See, e.g., ’039 patent, 49:56-52:30, 61:1-62:39;
Trail Tr. 72:14-25, 82:6-13, 197:4-9.

The '039 Patent's Family Is Directed to Dolastatin/Auristatin-Type Drugs



Related U.S. Application Data

Continuation of application No. 15/118,190, filed on Nov. 13, 2017, now Pat. No. 10,414,826, which is a continuation of application No. 15/188,843, filed on Jun. 21, 2016, now abandoned, which is a continuation of application No. 14/194,106, filed on Feb. 28, 2014, now abandoned, which is a continuation of application No. 13/098,391, filed on Apr. 29, 2011, now Pat. No. 8,703,714, which is a continuation of application No. 11/833,954, filed on Aug. 3, 2007, now Pat. No. 7,994,135, which is a division of application No. 10/983,340, filed on Nov. 5, 2004, now Pat. No. 7,498,298.

Provisional application No. 60/622,455, filed on Oct. 27, 2004, provisional application No. 60/598,899, filed on Aug. 4, 2004, provisional application No. 60/557,116, filed on Mar. 26, 2004, provisional application No. 60/518,534, filed on Nov. 6, 2003.

- This patent family's sole focus is on dolastatin/auristatins
  - All claims pursued prior to 2019 limited to dolastatin/auristatins
  - Each application's title refers to "monomethylvaline compounds capable of conjugation"

See, e.g., '039 Patent, (22), (60); U.S. Patent Nos. 7,498,298, Claim 1, 7,994,135, Claim 1, 8,703,714, Claim 36; 10,414,826, Claim 18.

Baxalta Inc. v. Genentech Inc. Is Inapposite

- Seagen relies on *Baxalta* to argue that Defendants' reliance on Section 9.4's lexicography is "in isolation from the rest of the patent"

- Unlike *Baxalta*, the '039 patent is entirely consistent with the lexicography in Column 71 for "drug moiety"
  - Title
  - Abstract
  - 40 Sheets of Figures
  - Background: "clear need in the art for dolastatin/auristatin derivatives . . ."
  - Summary of the Invention
  - All embodiments

See Seagen Reply Br. at 2.

"A Clear Need in the Art for Dolastatin/Auristatin Derivatives" Does Not Create a Conflict Under *Baxalta*

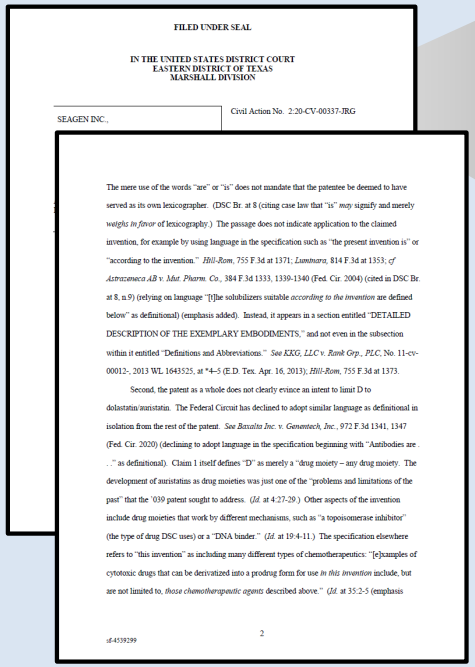
- Seagen's Reply incorrectly states that "[t]he development of auristatins as drug moieties was just one of the 'problems and limitations of the past' that the '039 patent sought to address"

- The patent actually states is that "there is a clear need in the art for dolastatin/auristatin derivatives" that are improved
  - For example, the patent references problems with toxicity and therapeutic efficiency of prior dolastatin/auristatin derivatives
  - The patent purports to address those, and other limitations and problems of the past, in light of the stated need for improved dolastatin/auristatin derivatives

See, e.g., '039 patent, 4:25-29.

Chemotherapeutic Agents "That Work By Different Mechanisms" Do Not Create a Conflict Under *Baxalta*

- Seagen's citation to alleged "drug moieties that work by different mechanisms" misleadingly revises the specification to include the term "drug moiety" where it does not appear



FILED UNDER SEAL

IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

SEAGEN INC.,

Civil Action No. 2:20-CV-00337-JRG

The mere use of the words "are" or "is" does not mandate that the patentee be deemed to have served as its own lexicographer. (DSC Br. at 8 (citing case law that "is" *may* signify and merely *weighs in favor* of lexicography.) The passage does not indicate application to the claimed invention, for example by using language in the specification such as "the present invention is" or "according to the invention." *Hill-Rom*, 755 F.3d at 1371; *Luminara*, 814 F.3d at 1353; *cf Astrazeneca AB v. Mut. Pharm. Co.*, 384 F.3d 1333, 1339-1340 (Fed. Cir. 2004) (cited in DSC Br. at 8, n.9) (relying on language "[t]he solubilizers suitable *according to the invention* are defined below" as definitional) (emphasis added). Instead, it appears in a section entitled "DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS," and not even in the subsection within it entitled "Definitions and Abbreviations." *See KXG, LLC v. Ramk Grp., PLC*, No. 11-cv-00012-, 2013 WL 1643525, at *4–5 (E.D. Tex. Apr. 16, 2013); *Hill-Rom*, 755 F.3d at 1373.

Second, the patent as a whole does not clearly evince an intent to limit D to dolastatin/auristatin. The Federal Circuit has declined to adopt similar language as definitional in isolation from the rest of the patent. *See Baxalta Inc. v. Genentech, Inc.*, 972 F.3d 1341, 1347 (Fed. Cir. 2020) (declining to adopt language in the specification beginning with "Antibodies are . . ." as definitional). Claim 1 itself defines "D" as merely a "drug moiety – any drug moiety. The development of auristatins as drug moieties was just one of the "problems and limitations of the past" that the '039 patent sought to address. (*Id.* at 4:27-29.) Other aspects of the invention include drug moieties that work by different mechanisms, such as "a topoisomerase inhibitor" (the type of drug DSC uses) or a "DNA binder." (*Id.* at 19:4-11.) The specification elsewhere refers to "this invention" as including many different types of chemotherapeutics: "[e]xamples of cytotoxic drugs that can be derivatized into a prodrug form for use *in this invention* include, but are not limited to, *those chemotherapeutic agents* described above." (*Id.* at 35:2-5 (emphasis

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2

See Seagen Reply Br. at 2.

Other aspects of the invention include drug moieties that work by different mechanisms, such as "a topoisomerase inhibitor" (the type of drug DSC uses) or a "DNA binder." (*Id.* at 19:4-11.)

In another aspect, the invention includes a pharmaceutical composition comprising an effective amount of the antibody-drug conjugate compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, carrier or excipient. The composition may further comprise a therapeutically effective amount of chemotherapeutic agent such as a tubulin-forming inhibitor, a topoisomerase inhibitor, and a DNA binder.

US010808039B2

(12) **United States Patent**
Doronina et al.

(10) **Patent No.: US 10,808,039 B2**
(45) **Date of Patent: Oct. 20, 2020**

(54) **MONOMETHYLVALINE COMPOUNDS CAPABLE OF CONJUGATION TO LIGANDS**

(71) Applicant: **SEATTLE GENETICS, INC.**, Bothell, WA (US)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

US 10,808,039 B2

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'039 patent, 19:4-11.

"Chemotherapeutic Agent" and "Prodrug" Do Not Create a Conflict Under *Baxalta*

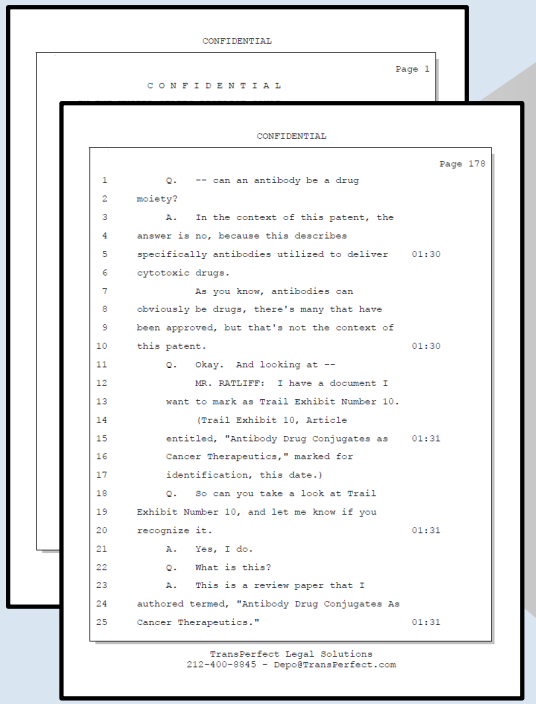
- The specification discloses "chemotherapeutic agents" and "prodrugs" thereof for use ***in combination with*** alleged compounds of the invention:
  - Col. 19:4-11 ("may further comprise a . . . chemotherapeutic agent")
  - Col. 161:15-16 ("administered concurrently with the chemotherapeutic agent")
  - Col. 161:60-64 ("administering . . . an Exemplary Conjugate and another therapeutic agent that is an anti-cancer agent")
  - Col. 34:50-35:5 (prodrugs are precursors or derivatives of such cytotoxic drugs)

See Seagen Reply Br. at 2-3; *see also* '039 patent, 34:50-35:5.

Seagen's Declarant Contradicts Seagen's Proposed Construction

- In deposition, Dr. Trail disagreed that "drug moiety" can be construed to mean "any drug moiety" as Seagen proposes

See Seagen Reply Br. at 2; Trail Tr. 178:1-10.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Page 1

C O N F I D E N T I A L

CONFIDENTIAL

Page 178

Q. -- can an antibody be a drug moiety?
A. In the context of this patent, the answer is no, because this describes specifically antibodies utilized to deliver cytotoxic drugs. 01:30
As you know, antibodies can obviously be drugs, there's many that have been approved, but that's not the context of this patent. 01:30
Q. Okay. And looking at --
MR. RATLIFF: I have a document I want to mark as Trail Exhibit Number 10.
(Trail Exhibit 10, Article entitled, "Antibody Drug Conjugates as Cancer Therapeutics," marked for identification, this date.) 01:31
Q. So can you take a look at Trail Exhibit Number 10, and let me know if you recognize it. 01:31
A. Yes, I do.
Q. What is this?
A. This is a review paper that I authored termed, "Antibody Drug Conjugates As Cancer Therapeutics." 01:31

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212-400-8845 - Depo@TransPerfect.com

Q. -- can an antibody be a drug moiety?

A. In the context of this patent, the answer is no, because this describes specifically antibodies utilized to deliver cytotoxic drugs.

As you know, antibodies can obviously be drugs, there's many that have been approved, but that's not the context of this patent.

Disputed Claim Terms

Drug Moiety

Spacer Unit and Self-Immolative Spacer

Drug-Linker Issues

Intracellularly Cleaved

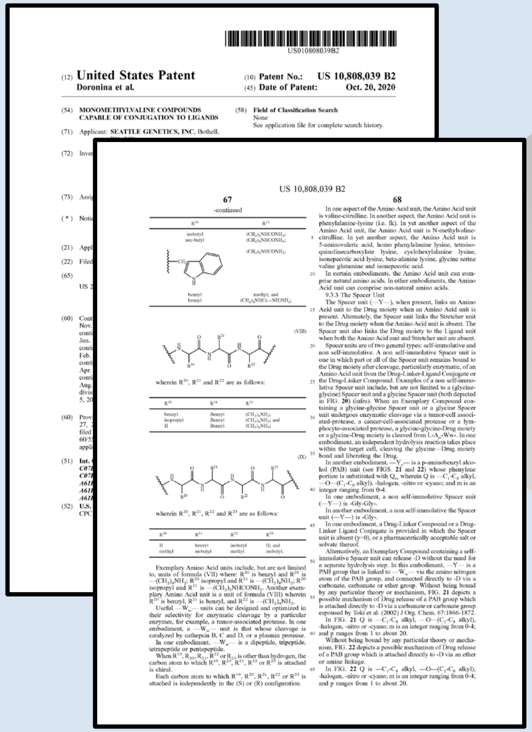
Options Presented In This *Markman* Dispute

The Spacer Unit: "Y is a Spacer unit"

Defendants' Construction	Seagen's Construction
"one or more atoms that links W_w to a nitrogen atom of D, the drug moiety"	Plain meaning/no construction is necessary. Alternatively, "Y is a unit that links the amino acid unit to a drug"

The Patent's Description of "Spacer Unit"

- The "Spacer unit" links the Drug moiety (or "Drug unit") to the Amino Acid unit (W_w).


(12) United States Patent
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(71) Applicant: SEATTLE GENETICS, INC., Bothell,

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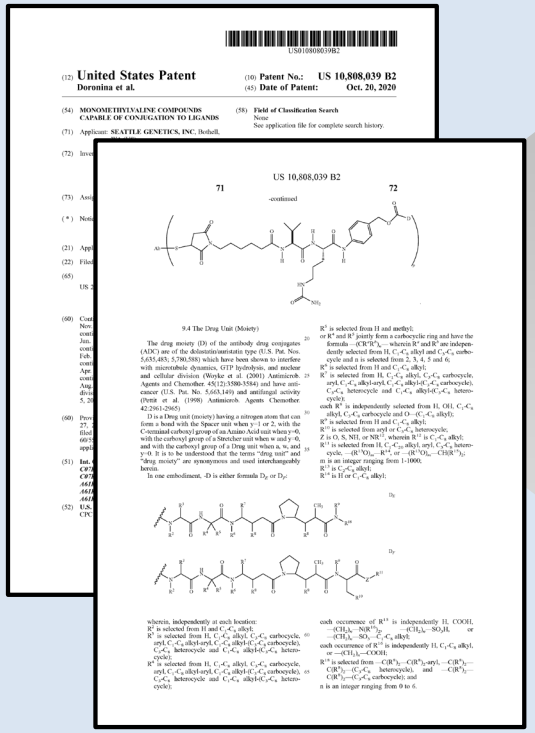
9.3.3 The Spacer Unit

The Spacer unit (—Y—), when present, links an Amino Acid unit to the Drug moiety when an Amino Acid unit is present. Alternately, the Spacer unit links the Stretcher unit to the Drug moiety when the Amino Acid unit is absent. The Spacer unit also links the Drug moiety to the Ligand unit when both the Amino Acid unit and Stretcher unit are absent.

'039 patent, 68:13-19.

The Patent's Description of "Spacer Unit"

- The "Drug unit," in turn, has a nitrogen atom that forms a bond with the "Spacer unit."



US10808039B2

(12) **United States Patent**
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(10) **Patent No.: US 10,808,039 B2**
(45) **Date of Patent: Oct. 20, 2020**

(54) **MONOMETHYLVALINE COMPOUNDS CAPABLE OF CONJUGATION TO LIGANDS**

(58) **Field of Classification Search**
None
See application file for complete search history.

(71) Applicant: **SEATTLE GENETICS, INC.**, Bothell,

US 10,808,039 B2

71 72

-continued

9.4 The Drug Unit (Moiety)

The drug moiety (D) of the antibody drug conjugates (ADC) are of the dolastatin/auristatin type (U.S. Pat. Nos. 5,635,483; 5,780,588) which have been shown to interfere with microtubule dynamics, GTP hydrolysis, and nuclear and cellular division (Woyke et al. (2001) Antimicrob. Agents and Chemother. 45(12):3580-3584) and have anti-cancer (U.S. Pat. No. 5,663,149) and antifungal activity (Pettit et al. (1998) Antimicrob. Agents Chemother. 42:2961-2965)

D is a Drug unit (moiety) having a nitrogen atom that can form a bond with the Spacer unit when y=1 or 2, with the C-terminal carboxyl group of an Amino Acid unit when y=0, with the carboxyl group of a Stretcher unit when w and y=0, and with the carboxyl group of a Drug unit when a, w, and y=0. It is to be understood that the terms "drug unit" and "drug moiety" are synonymous and used interchangeably herein.

In one embodiment, -D is either formula D_E or D_F:

wherein, independently at each location:
R^2 is selected from H and C_1-C_8 alkyl;
R^3 is selected from H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C$_3$-C_8 carbocycle), C_3-C_8 heterocycle and C_1-C_8 alkyl-(C$_3$-C_8 heterocycle);
R^4 is selected from H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C$_3$-C_8 carbocycle), C_3-C_8 heterocycle and C_1-C_8 alkyl-(C$_3$-C_8 heterocycle);

R^5 is selected from H and methyl;
or R^4 and R^5 jointly form a carbocyclic ring and have the formula $-(CR^{44}R^{45})_n-$ wherein R^{44} and R^{45} are independently selected from H, C_1-C_8 alkyl and C_3-C_8 carbocycle and n is selected from 2, 3, 4, 5 and 6;
R^6 is selected from H and C_1-C_8 alkyl;
R^7 is selected from H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C$_3$-C_8 carbocycle), C_3-C_8 heterocycle and C_1-C_8 alkyl-(C$_3$-C_8 heterocycle);
each R^8 is independently selected from H, OH, C_1-C_8 alkyl, C_3-C_8 carbocycle and O-(C_1-C_8 alkyl);
R^9 is selected from H and C_1-C_8 alkyl;
R^{10} is selected from aryl or C_3-C_8 heterocycle;
Z is O, S, NH, or NR^{12}, wherein R^{12} is C_1-C_8 alkyl;
R^{11} is selected from H, C_1-C_{20} alkyl, aryl, C_3-C_8 heterocycle, $-(R^{13}O)_m-R^{14}$, or $-(R^{13}O)_m-CH_2(R^{13})_2$;
m is an integer ranging from 1-1000;
R^{13} is C_2-C_8 alkyl;
R^{14} is H or C_1-C_8 alkyl;

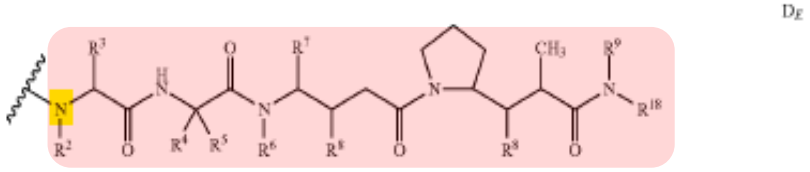
each occurrence of R^{15} is independently H, COOH, $-(CH_2)_n-N(R^{16})_2$, $-(CH_2)_n-SO_3H$, or $-(CH_2)_n-SO_3-C_1$-C_8 alkyl;
each occurrence of R^{16} is independently H, C_1-C_8 alkyl, or $-(CH_2)_n-COOH$;
R^{17} is selected from $-C(R^8)_2-C(R^8)_2$-aryl, $-C(R^8)_2-C(R^8)_2-$(C$_3$-C_8 heterocycle), and $-C(R^8)_2-C(R^8)_2-$(C$_3$-C_8 carbocycle); and
n is an integer ranging from 0 to 6.

D is a Drug unit (moiety) having a nitrogen atom that can form a bond with the Spacer unit when y=1 or 2, with the C-terminal carboxyl group of an Amino Acid unit when y=0, with the carboxyl group of a Stretcher unit when w and y=0, and with the carboxyl group of a Drug unit when a, w, and y=0. It is to be understood that the terms "drug unit" and "drug moiety" are synonymous and used interchangeably herein.

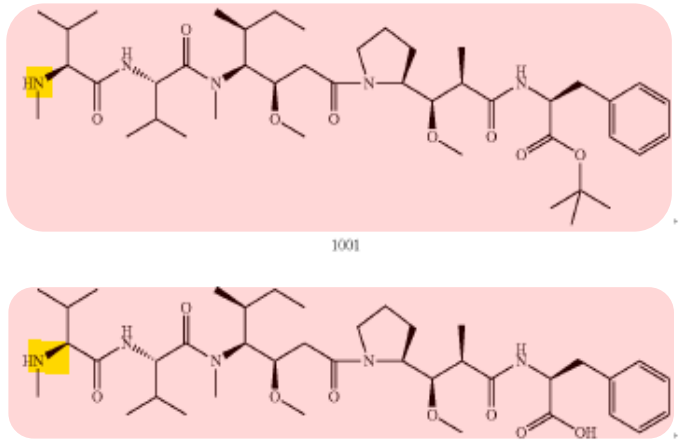
'039 patent, 71:30-37.

Exemplary Embodiments

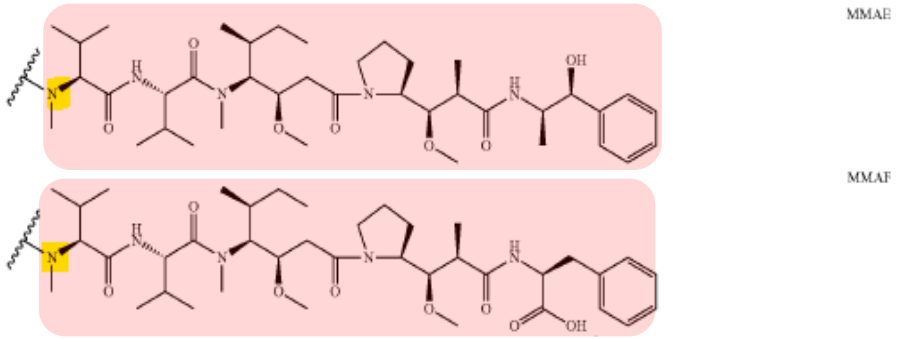
Each and every exemplary drug moiety in the patent contains a nitrogen atom that links to the Spacer unit.



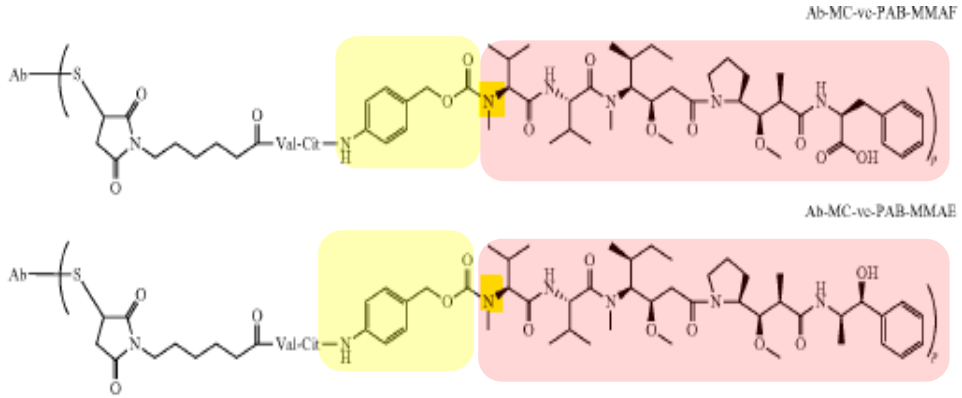
'039 patent, 6:50-67.



'039 patent, 53:16-58:18.



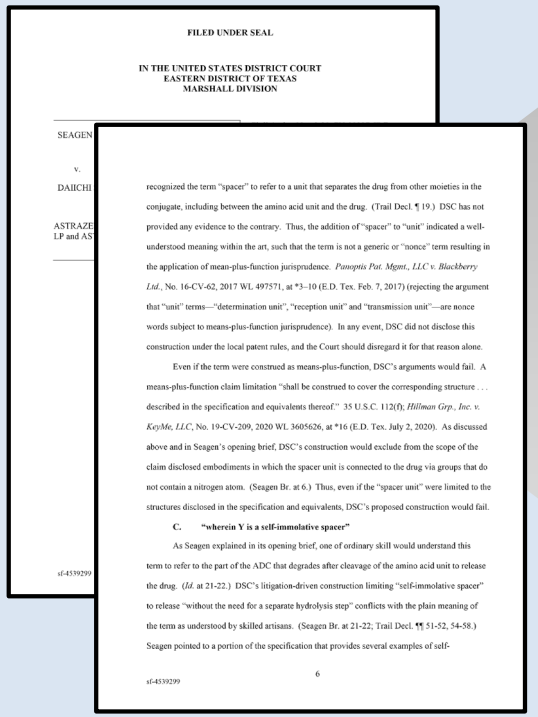
'039 patent, 74:12-78:16.



'039 patent, 61:1-62:40.

Seagen Accuses Defendants of Excluding Embodiments

Defendants' Proposed Construction:
"one or more atoms that links W_w to a nitrogen atom of D, the drug moiety"



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recognized the term "spacer" to refer to a unit that separates the drug from other moieties in the conjugate, including between the amino acid unit and the drug. (Trail Decl. ¶ 19.) DSC has not provided any evidence to the contrary. Thus, the addition of "spacer" to "unit" indicated a well-understood meaning within the art, such that the term is not a generic or "nonce" term resulting in the application of mean-plus-function jurisprudence. *Panoptis Pat. Mgmt., LLC v. Blackberry Ltd.*, No. 16-CV-62, 2017 WL 497571, at *3–10 (E.D. Tex. Feb. 7, 2017) (rejecting the argument that "unit" terms—"determination unit", "reception unit" and "transmission unit"—are nonce words subject to means-plus-function jurisprudence). In any event, DSC did not disclose this construction under the local patent rules, and the Court should disregard it for that reason alone.

Even if the term were construed as means-plus-function, DSC's arguments would fail. A means-plus-function claim limitation "shall be construed to cover the corresponding structure . . . described in the specification and equivalents thereof." 35 U.S.C. 112(f); *Hillman Grp., Inc. v. KeyMe, LLC*, No. 19-CV-209, 2020 WL 3605626, at *16 (E.D. Tex. July 2, 2020). As discussed above and in Seagen's opening brief, DSC's construction would exclude from the scope of the claim disclosed embodiments in which the spacer unit is connected to the drug via groups that do not contain a nitrogen atom. (Seagen Br. at 6.) Thus, even if the "spacer unit" were limited to the structures disclosed in the specification and equivalents, DSC's proposed construction would fail.

C. "wherein Y is a self-immolative spacer"

As Seagen explained in its opening brief, one of ordinary skill would understand this term to refer to the part of the ADC that degrades after cleavage of the amino acid unit to release the drug. (*Id.* at 21-22.) DSC's litigation-driven construction limiting "self-immolative spacer" to release "without the need for a separate hydrolysis step" conflicts with the plain meaning of the term as understood by skilled artisans. (Seagen Br. at 21-22; Trail Decl. ¶¶ 51-52, 54-58.) Seagen pointed to a portion of the specification that provides several examples of self-

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As discussed above and in Seagen's opening brief, DSC's construction would exclude from the scope of the claim disclosed embodiments in which the spacer unit is connected to the drug via groups that do not contain a nitrogen atom. (Seagen Br. at 6.)

Seagen Reply Br. at 6.

Defendants' Description is Consistent with Exemplary Embodiments

Defendants' Proposed Construction:
"one or more atoms that links W_w to a nitrogen atom of D, the drug moiety"

Figure 21

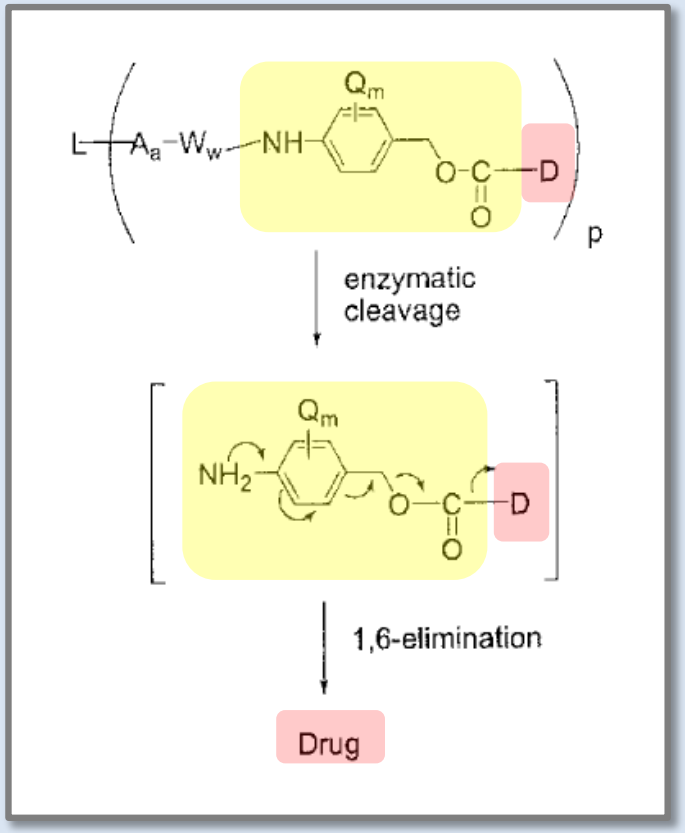
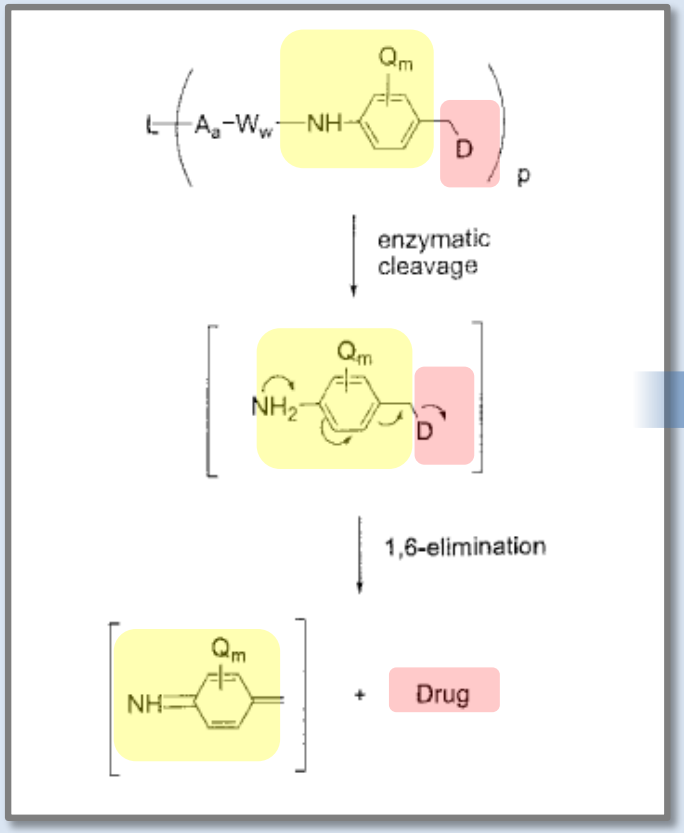


Figure 22



D, the Drug moiety, in Figures 21 and 22 would link to the Spacer unit via a nitrogen atom located on D.

Williamson v. Citrix Online, LLC, 792 F.3d 1339 (Fed. Cir. 2015) (en banc)

- "[F]ailure to use the word 'means' . . . creates a rebuttable presumption." But the presumption is not strong. *See id.* at 1348.
- The presumption against means-plus-function is overcome when "the claim term fails to 'recite[] sufficiently definite structure' or else recites 'function without reciting sufficient structure for performing that function.'" *Id.*
- "Nonce" words can operate as a substitute for "means" and trigger application of § 112 ¶ 6. *Id.* at 1350. Modifiers before a "nonce" word must describe a sufficiently definite structure to avoid application of § 112 ¶ 6. *Id.* at 1351.

Diebold Nixdorf, Inc. v. ITC, 899 F.3d 1291 (Fed. Cir. 2018)

- "Cheque standby unit" is subject to § 112 ¶ 6.
- "The standard by which we determine whether § 112, para. 6 applies 'is whether the words of the claim are understood by persons of ordinary skill in the art to have a sufficiently definite meaning as the name for structure.'" *Id.* at 1297.

Diebold Nixdorf, Inc. v. ITC, 899 F.3d 1291 (Fed. Cir. 2018)

- "[T]he claims describe the term 'cheque standby unit' **solely in relation to its function and location in the apparatus**."
- "**[T]he word 'unit,' . . . does not, standing alone, connote any particular structure**. Nor is sufficient structure imparted by modifying the word 'unit' with the words 'cheque' and 'standby' or by specifying the location of the 'cheque standby unit.'" *Id.* at 1301.
- "Nor does the fact the 'cheque standby unit' must be formed on the main transfer unit between the first and second gates offer any guidance 'that might inform the structural character of the limitation-in-question or otherwise impart structure' to the term as recited in the claims." *Id.* at 1298–99.

Diebold Nixdorf, Inc. v. ITC, 899 F.3d 1291 (Fed. Cir. 2018)

- "[T]he Commission credited Dr. Howard's expert testimony in determining that the term 'cheque standby unit' connotes sufficiently definite meaning as the name for structure to persons of ordinary skill in the art." *Id.* at 1299.
- "The Commission and Hyosung raise two arguments in response. First, they contend that, because Diebold failed to present affirmative evidence of how a person of ordinary skill would understand the claim language, Diebold failed to rebut the presumption against the application of § 112, para. 6. Second, they submit both that the Commission was entitled to credit Dr. Howard's testimony, and that such testimony was sufficient to demonstrate that the term 'cheque standby unit' had a structural meaning to persons of skill in the art at the relevant time." *Id.*

Diebold Nixdorf, Inc. v. ITC, 899 F.3d 1291 (Fed. Cir. 2018)

- "First, none of our cases mandate that a party seeking to overcome the presumption against application of § 112, para. 6 can only do so by presenting extrinsic evidence that one of ordinary skill would fail to understand that a term connotes a definite structure." *Id.* at 1299.

Diebold Nixdorf, Inc. v. ITC, 899 F.3d 1291 (Fed. Cir. 2018)

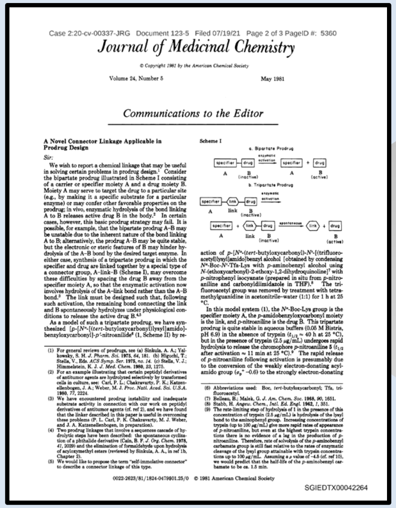
- Patentee's expert testified that a person of ordinary skill in the art "would understand the unit must be 'comprised of well-known components for holding cheques in a standby configuration pending user confirmation of the deposit,' and must 'interface with the main transfer path.'" *Id.* at 1300.
- "Nowhere in [Dr. Howard's] testimony does he explain with any degree of definiteness what structure or class of structures a person of ordinary skill would understand the term to encompass." *Id.*
- "He likewise **failed to offer any structural limitation that might serve to cabin the scope of the functional term**." *Id.* at 1300–01.
- "In essence, Dr. Howard did little more than opine that a skilled artisan would understand the functional term 'cheque standby unit' to be any structure capable of performing the claimed function." *Id.* at 1301.

Seagen's Cited Cases Are Inapposite

***Panoptis Patent Mgmt., LLC v. Blackberry Ltd.*, No. 2:16-CV-62-JRG-RSP, 2017 WL 497571 (E.D. Tex. Feb. 7, 2017)**

- "Determination unit" was not a means-plus-function limitation because it connoted a structure.
- "In the context of a mobile-communication-system patent and a claim to a 'mobile station apparatus,' the 'determination unit' is a specially configured electronic circuit." *Id.* at *5.
- "[T]ogether, the claims require the 'determination unit' to be connected to the 'reception unit' in such a way as to have access to the allocation information the 'determination unit' uses to determine the resource of downlink. The claim also **provides structure through the details of indices of the allocation information**—'the indices of a plurality of the consecutive resource blocks are respectively associated with a plurality of the resources which are different in a frequency domain.'" *Id.*

Seagen's Cited Papers Do Not Impose Structural Limits on "Spacer"



In either case, synthesis of a tripartate prodrug in which the specifier and drug are linked together by a special type of a connector group, A-link-B (Scheme I), may overcome these difficulties by spacing the drug B away from the specifier moiety A, so that the enzymatic activation now involves hydrolysis of the A-link bond rather than the A-B bond.

Carl 1981 (SGIEDTEX00042264; Ex. 3 to Seagen Opening Br.).

The incorporation of a self-immolative spacer between the dipeptide and the drug ensures access to the site of cleavage by lysosomal enzymes such as cathepsin B (16).

Ajaj 2009 (SGIEDTEX00042203; Ex. 4 to Seagen Opening Br.).

Seagen's Cited Papers Do Not Impose Structural Limits on "Spacer"

Case 2:20-cv-00337-JRG Document 123-8 Filed 07/19/21 Page 2 of 5 PageID #: 5407

Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 1529–1532

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Doxorubicin Immunoconjugates Containing Bivalent, Lysosomally-Cleavable Dipeptide Linkages

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Received 13 November 2001; accepted 15 February 2002

Abstract—Bivalent doxorubicin (DOX)-dipeptides (**16a–c**) were prepared and conjugated to the monoclonal antibody BR96. The dipeptides are cleaved by lysosomal proteases following internalization of the resulting immunoconjugates. Conjugate **18b** demonstrated antigen-specific in vitro tumor cell killing activity ($IC_{50} = 0.2\ nM$) that was equipotent to DOX with a near doubling of drug molecules/MAb. Size exclusion chromatography showed **18b** to be a monovalent dimer that was formed immediately upon conjugation.

The success of antigen-dependent drug delivery to target tumor cell populations can be limited by the cell surface density of expressed antigen by saturation of the receptors with immunoconjugate that is endocytosed at a given rate.[1] In this regard, the more drug molecules an immunoconjugate is able to carry without compromising tumor localization, drug release, and aqueous solubility the better. One way of increasing drug loading without coating the surface of a monoclonal antibody (MAb) with (usually lipophilic) drug moieties is to use polyvalent linkers in conjunction with carefully controlled conjugation methods. Herein we report the synthesis of branched drug-dipeptide linker compounds that can be conjugated to free thiol groups generated on MAbs by treatment with limiting amounts of dithiothreitol (DTT).[2] The dipeptides are cleaved by lysosomal proteases following internalization of the resulting immunoconjugates.[3] The liberation of active drug by these dipeptide conjugates requires the presence of a self-immolative *p*-aminobenzyloxycarbonyl (PABC) spacer,[4] presumably because of steric constraints in the enzyme active site.[5]

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‡Present address: Bayer Research Center, 400 Morgan Lane, West Haven, CT 06516-4175, USA.

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PII: S0960-894X(02)00194-4

Design and Synthesis

To make the linkers as hydrophilic as possible, we wanted to minimize their size while ensuring that the site of desired proteolytic cleavage was unencumbered so that liberation of free drug could occur as rapidly as with single-chain dipeptide linkers. Previous hydrazone-containing branched linkers used glutamic acid as the branching device.[5] However, to generate symmetrical linkers and to avoid the issue of chirality we chose to use iminodiacetyl (IDA) and iminodipropionyl (IDP) units in order to vary the distance between the branch point and the dipeptide. The maleimidoethyl-containing intermediates **7a** and **7b** were prepared as shown in Scheme 1. Mono-protected ethylenediamine **3** was prepared in 55% overall yield by treatment with 2 equiv of benzyloxycarbonyl chloride followed by partial acid-olysis in conced HCl/acetic acid.[6] Alkylation using either *t*-butyl bromoacetate or *t*-butyl acrylate, followed by hydrogenolysis in the presence of acetic acid gave the sensitive amino diesters **5a** and **5b**. These were immediately treated with maleic anhydride followed by TMSCl-mediated cyclization to give the maleimidoesters **6a** and **6b** in ca. 60% yield. Significant decomposition occurred when deprotection was attempted with TFA or HCl in dioxane. However, overnight stirring with 3 equiv of *p*-toluenesulfonic acid (TsOH) in CH_2Cl_2 provided the diacid ammonium salts **7a** and **7b**. In each case, a solid precipitate was formed

SGIEDTX00042254

Herein we report the synthesis of branched drug-dipeptide linker compounds that can be conjugated to free thiol groups generated on MAbs by treatment with limiting amounts of dithiothreitol (DTT). The dipeptides are cleaved by lysosomal proteases following internalization of the resulting immunoconjugates. The liberation of active drug by these dipetide conjugates requires the presence of a self-immolative *p*-aminobenzyloxycarbonyl (PABC) spacer, presumably because of steric constraints in the enzyme active site.

Dubowchik 2002 (SGIEDTEX00042254; Ex. 6 to Seagen Opening Br.).

Robert Bosch, LLC v. Snap-On Inc., 769 F.3d 1094 (Fed. Cir. 2014)

- "[M]erely listing examples of possible structures is insufficient to avoid invocation of § 112, ¶ 6. Indeed, means-plus-function language that defines a category in functional terms will typically cover examples of structures that fall within it. This is not a basis for distinguishing structural language from § 112, ¶ 6 language." *Id.* at 1101; *see also MTD Prods. Inc. v. Iancu*, 933 F.3d 1336, 1343 (Fed. Cir. 2019).

Seagen's Construction Imposes No Structural Limits

Q. Are you taking the position that a spacer unit could be anything, any number of atoms?

* * *

A. So in many ways this comes back to producing an ADC by conjugation versus producing an ADC that has function and will release drug. So as you know, the purpose of the spacers are for stability of the ADC, and they're also to enable enzymatic cleavage of the linkers. So any spacer of any size that can fulfill those definition would have the potential to be biologically active. Anything could be thrown in as a spacer. It just would not necessarily produce a function of ADC.

Trail Tr. 271:14-272:5.

Seagen's Construction

Plain meaning/no construction is necessary.

Alternatively, "Y is a unit that links the amino acid unit to a drug"

Seagen Has Rejected Every Attempt to Impose Structure on the Claim Term

[3] DSC also proposes that the term be construed to include the limitation "one or more atoms" in place of the commonly understood term "unit." The specification of the patent does not define the term "unit" as being "one or more atoms," so there is no reason to deviate from the plain and ordinary meaning. Nor is there any dispute that DSC's construction of "unit" would resolve. Hence, the inclusion of this unnecessary verbiage should be rejected.

Seagen Opening Br. at 7 n.3.

DSC's proposal introduces a specialized meaning to the term "unit" which is inappropriate given the intrinsic and extrinsic evidence. Although molecules do contain atoms, the patent doesn't refer to a "unit" as being "one or more atoms." The atomic structure of a spacer is not at issue in this case and DSC's proposal introduces ambiguity.

Trail Declaration ¶ 21.

Seagen's Construction
Plain meaning/no construction is necessary. Alternatively, "Y is a unit that links the amino acid unit to a drug"

Construing a Means-Plus-Function Claim Term

Step One:

Identify the claimed function

- Dr. Trail states that the spacer unit's functions include enhancing stability and supporting enzymatic cleavage to release free drug

> Q. And I'm trying to figure out what spacers are within the scope of the '039 patent claims. Sitting here today, do you believe there is any limitation whatsoever as to the type of spacers that are within scope of the '039 patent claims?
>
> * * *
>
> A. Once again, I looked at what was exemplified here. I did not do an analysis of everything that could function as a spacer. What's claimed here, as I read it, in the patent, is a spacer unit which is zero, one or two. So if it meets that definition, and it is able to improve stability and/or more efficiently enable enzymatic cleavage, I believe it is covered here. But I have not done that analysis to tell you what those structures are.

Trail Tr. 272:6-24.

Construing a Means-Plus-Function Claim Term

Step Two:

Determine what structure, if any, disclosed in the specification corresponds to the claimed function

- Dr. Trail conceded she had not "done the analysis to tell you what those structures are."

Q. And I'm trying to figure out what spacers are within the scope of the '039 patent claims. Sitting here today, do you believe there is any limitation whatsoever as to the type of spacers that are within scope of the '039 patent claims?

* * *

A. Once again, I looked at what was exemplified here. I did not do an analysis of everything that could function as a spacer. What's claimed here, as I read it, in the patent, is a spacer unit which is zero, one or two. So if it meets that definition, and it is able to improve stability and/or more efficiently enable enzymatic cleavage, I believe it is covered here. But I have not done that analysis to tell you what those structures are.

Trail Tr. 272:6-24.

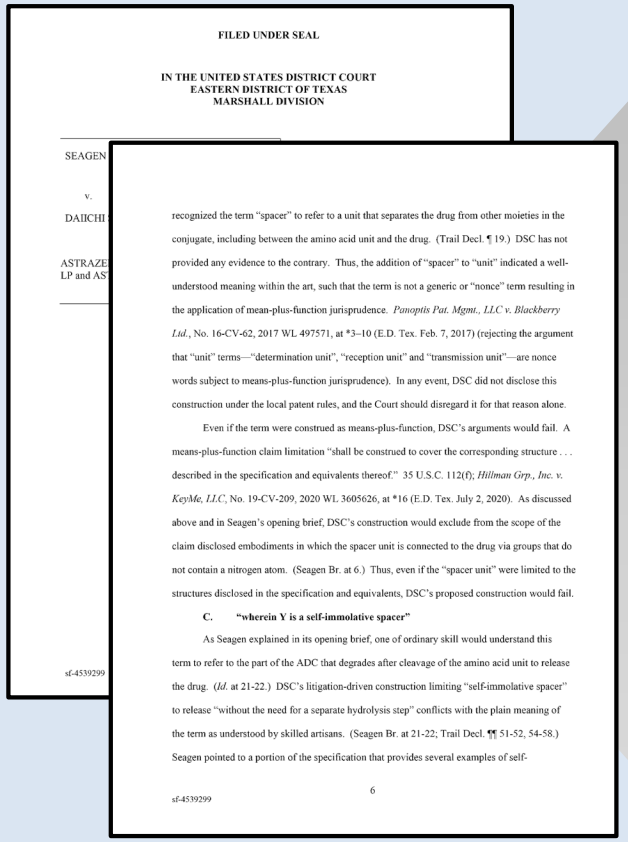
Q. Understood. Now, does the patent provide any guidance as to how to determine spacers that meet those functional requirements that you just described?

* * *

A. No.

Trail Tr. 273:13-18.

The Cases Seagen Cites Are Inapposite



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C. "wherein Y is a self-immolative spacer"

As Seagen explained in its opening brief, one of ordinary skill would understand this term to refer to the part of the ADC that degrades after cleavage of the amino acid unit to release the drug. (*Id.* at 21-22.) DSC's litigation-driven construction limiting "self-immolative spacer" to release "without the need for a separate hydrolysis step" conflicts with the plain meaning of the term as understood by skilled artisans. (Seagen Br. at 21-22; Trail Decl. ¶¶ 51-52, 54-58.) Seagen pointed to a portion of the specification that provides several examples of self-

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But there is nothing improper about functional claim language. *Nevro Corp. v. Bos. Sci. Corp.*, 955 F.3d 35, 39 (Fed. Cir. 2020); *Cox Commc'ns, Inc. v. Sprint Commc'n Co. LP*, 838 F.3d 1224, 1232 (Fed. Cir. 2016). Nor does the mere presence of functional language convert a claim term into a means-plus-function term absent the use of the word "means." *Zeroclick, LLC v. Apple Inc.*, 891 F.3d 1003, 1008 (Fed. Cir. 2018) ("[T]he mere fact that the disputed limitations incorporate functional language does not automatically convert the words into means for performing such functions."); *Samsung Elecs. Am., Inc. v. Prisua Eng'g Corp.*, 948 F.3d 1342, 1353 (Fed. Cir. 2020) (rebuttal presumption that section 112, paragraph 6 applies in the absence of "means for"). In fact, DSC's own proposed construction is functional: "one or more atoms *that links* W_w to a nitrogen atom of D." (DSC Br. at 14 (emphasis added).)

Seagen Reply Br. at 5-6.

Seagen's Cited Cases Are Inapposite

Nevro Corp. v. Bos. Sci. Corp.,
955 F.3d 35 (Fed. Cir. 2020)

- Seagen cites this case for the proposition that functional claim language is not per se improper. Defendants agree
- However, the portion of *Nevro* Seagen cites (955 F.3d at 39) does not discuss a means-plus-function limitation, just functional language that imposes a function on a method claim

Seagen's Cited Cases Are Inapposite

***Cox Commc'ns, Inc. v. Sprint Commc'n Co. LP*, 838 F.3d 1224 (Fed. Cir. 2016)**

- "We note, however, that in the context of 35 U.S.C. § 112, ¶ 6, we require that, if a patentee writes his claims in 'means-plus-function' form, **he must 'disclose the particular structure that is used to perform the recited function**.' *Blackboard, Inc. v. Desire2Learn, Inc.*, 574 F.3d 1371, 1385 (Fed. Cir. 2009). This is intended to avoid 'pure functional claiming,' where a patentee 'claim[s] all possible means of achieving a function.' *Id.* However**, by agreeing that 'processing system' is not a means-plus-function term, Cox has already conceded that 'processing system' itself recites sufficiently definite structure and there is no problem of 'pure functional claiming' here**."

Seagen's Cited Cases Are Inapposite

***Samsung Elecs. Am., Inc. v. Prisua Eng'g Corp.*, 948 F.3d 1342 (Fed. Cir. 2020)**

- "[T]the term 'digital processing unit' clearly serves as a stand-in for a 'general purpose computer' or a 'central processing unit,' each of which would be understood as a reference to structure in this case, not simply any device that can perform a particular function." *Id.* at 1354.
- The Board also contradicted itself. *Id.* ("The Board's treatment of the 'digital processing unit' limitation in claim 11 as structural in nature undermines its conclusion that the same term in claim 1 was functional and thus subject to analysis under section 112, paragraph 6.").

Meet & Confer Process

Seagen refused to clarify whether it believed its claim construction position imposed any structural limitation on the claim

Exhibit 3 to Defendants' Claim Construction Response Brief (DSC's Email of May 24, 2021 at 8:25 am)

Counsel:

We write concerning Seagen's disclosure pursuant to P.R. 4-2. There appear to be several places where we may be able to converge on agreement, or at least crystallize our disputes.

Y is a Spacer Unit

We understand you to contend that a "Spacer unit" is a "unit that links the amino acid unit to a drug." We assume you agree that the 'amino acid unit' is W_w, as identified in our proposed construction. Please confirm. Do you likewise agree that the Spacer unit must connect to a nitrogen atom of a drug?

Your proposed construction does not clarify what you mean by a "unit." Does this term impose any structural limitation on the claim? If so, how does it do so?

Meet & Confer Process

Seagen refused to clarify whether it believed its claim construction position imposed any structural limitation on the claim

Exhibit 3 to Defendants' Claim Construction Response Brief
(Seagen's Response of May 24, 2021 at 8:23 pm)

Counsel,

As to your position regarding "Y is a spacer unit," are you asking if we can agree to a construction as follows: "Y is a unit that links the amino acid unit, W_w, to a drug"? If not, it appears we are far apart.

We have reviewed the remainder of your positions and it doesn't appear that we are in agreement on those.

Best,
Teresa

Meet & Confer Process

Exhibit 3 to Defendants' Claim Construction Response Brief (DSC's Email of May 26, 2021 at 8:38 pm)

Counsel:

The point of our prior email was to confer pursuant to P.R. 4-2 in hopes of finding common ground or clarifying points of disagreement. Your response did not address the vast majority of our questions. Where possible, we have inferred that you disagree with us and have restated our understanding of the parties' dispute. If you believe any aspect of this does not accurately capture our disputes, please let us know promptly.

Y is a Spacer Unit

We are not proposing that "Y is a Spacer unit" be construed as "Y is a unit that links the amino acid unit, W_w, to a drug." From your response, we understand there to be two disputes: (1) what is a "unit"?; and (2) whether the "Spacer unit" must connect to a nitrogen atom. We had thought we would be able to resolve (1), as we imagined it non-controversial that the Spacer unit is "one or more atoms." But if you disagree with that, we would appreciate knowing what you contend a "unit" is, if not that, so we may assess your position in the hopes of reaching agreement.

Meet & Confer Process

Exhibit 3 to Defendants' Claim Construction Response Brief (Seagen's Response of June 1, 2021 at 1:56 pm)

Counsel,

We disagree with your characterizations of our positions below. We also don't see your positions as attempts to reach compromise, but rather to balloon the number of issues in dispute beyond the customary number for EDTX. In addition, we find your positions confusing, and unsupported by the intrinsic evidence. Please explain why they are correct.

If you'd like a further meet and confer, we are available Thursday between 10-12 or 1-3 pm PT.

Best,
Teresa

Meet & Confer Process

Exhibit 3 to Defendants' Claim Construction Response Brief (DSC's Response of June 2, 2021 at 3:54 pm)

Counsel,

We note your refusal to confer with us on the substance of the parties' positions, as reflected in the below email exchange. Your suggestion that we instead confer by phone the day before the parties' joint filing is due seems unlikely to provide us with sufficient time to confer with our client in Japan, but we can be available during the 1-2 pm PT window to discuss any proposed changes to the attached draft as we prepare to file on Friday. In advance of the call, please explain what about our positions you find confusing and what about our understanding of Seagen's positions you disagree with.

Best,
Mike

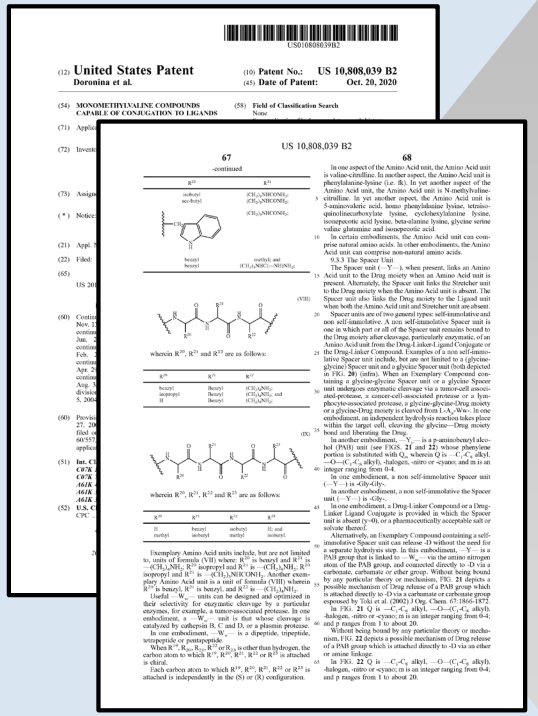
Options Presented In This *Markman* Dispute

The Spacer Unit: "wherein Y is a self-immolative spacer"

Defendants' Construction	Seagen's Construction
"wherein the drug moiety is released from Y without a separate hydrolysis step"	Plain meaning/no construction is necessary. Alternatively, "wherein Y is a spacer that degrades to release the drug after cleavage of the amino acid unit."

The Specification Distinguishes Between Two Types of Spacer Units

Non Self-Immolative Spacer

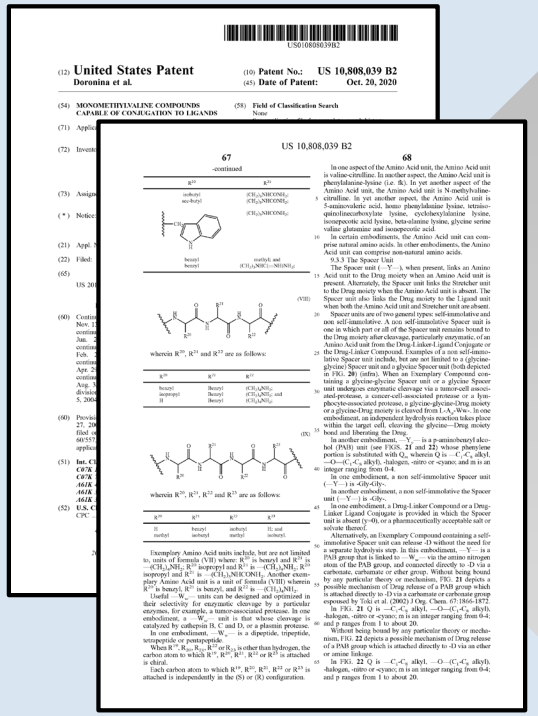


Spacer units are of two general types: self-immolative and non self-immolative. A non self-immolative Spacer unit is one in which part or all of the Spacer unit remains bound to the Drug moiety after cleavage, particularly enzymatic, of an Amino Acid unit from the Drug-Linker-Ligand Conjugate or the Drug-Linker Compound. Examples of a non self-immolative Spacer unit include, but are not limited to a (glycine-glycine) Spacer unit and a glycine Spacer unit (both depicted in FIG. 20) (infra). When an Exemplary Compound containing a glycine-glycine Spacer unit or a glycine Spacer unit undergoes enzymatic cleavage via a tumor-cell associated-protease, a cancer-cell-associated protease or a lymphocyte-associated protease, a glycine-glycine-Drug moiety or a glycine-Drug moiety is cleaved from L-A_a-W_w-. In one embodiment, an independent hydrolysis reaction takes place within the target cell, cleaving the glycine—Drug moiety bond and liberating the Drug.

'039 patent, 68:20-35.

The Specification Distinguishes Between Two Types of Spacer Units

Self-Immolative Spacer



(12) **United States Patent**
Doronina et al.

(10) **Patent No.: US 10,808,039 B2**
(45) **Date of Patent: Oct. 20, 2020**

(54) **MONOMETHYLVALINE COMPOUNDS CAPABLE OF CONJUGATION TO LIGANDS**

US 10,808,039 B2

67 -continued

68

wherein R^{20}, R^{21} and R^{22} are as follows:

wherein R^{20}, R^{21}, R^{22} and R^{23} are as follows:

Exemplary Amino Acid units include, but are not limited to, units of formula (VII) where: R^{20} is benzyl and R^{21} is $-(CH_2)_4NH_2$; R^{20} isopropyl and R^{21} is $-(CH_2)_4NH_2$; R^{20} isopropyl and R^{22} is $-(CH_2)_3NHCONH_2$. Another exemplary Amino Acid unit is a unit of formula (VIII) wherein R^{22} is benzyl, R^{21} is benzyl, and R^{22} is $-(CH_2)_4NH_2$.

Useful $-W_w-$ units can be designed and optimized in their selectivity for enzymatic cleavage by a particular enzymes, for example, a tumor-associated protease. In one embodiment, a $-W_w-$ unit is that whose cleavage is catalyzed by cathepsin B, C and D, or a plasmin protease.

In one embodiment, $-W_w-$ is a dipeptide, tripeptide, tetrapeptide or pentapeptide.

When R^{21}, R_{20}, R_{22}, R^{22} or R_{23} is other than hydrogen, the carbon atom to which R^{21}, R^{20}, R^{22}, R^{22} or R^{23} is attached is chiral.

Each carbon atom to which R^{20}, R^{21}, R^{22}, R^{23} or R^{23} is attached is independently in the (S) or (R) configuration.

In one aspect of the Amino Acid unit, the Amino Acid unit is valine-citrulline. In another aspect, the Amino Acid unit is phenylalanine-lysine (i.e. fk). In yet another aspect of the Amino Acid unit, the Amino Acid unit is N-methylvaline-citrulline. In yet another aspect, the Amino Acid unit is 5-aminovaleric acid, homo phenylalanine lysine, tetrasio-quinolinecarboxylyne lysine, cyclohexylalanine lysine, isoserpeotic acid lysine, beta-alanine lysine, glycine serine valine glutamine and isoaspeotic acid.

In certain embodiments, the Amino Acid unit can comprise natural amino acids. In other embodiments, the Amino Acid unit can comprise non-natural amino acids.

9.3.3 The Spacer Unit

The Spacer unit (—Y—), when present, links an Amino Acid unit to the Drug moiety when an Amino Acid unit is present. Alternately, the Spacer unit links the Stretcher unit to the Drug moiety when the Amino Acid unit is absent. The Spacer unit also links the Drug moiety to the Ligand unit when both the Amino Acid unit and Stretcher unit are absent.

Spacer units are of two general types: self-immolative and non self-immolative. A non self-immolative Spacer unit is one in which part or all of the Spacer unit remains bound to the Drug moiety after cleavage, particularly enzymatic, of an Amino Acid unit from the Drug-Linker-Ligand Conjugate or the Drug-Linker Compound. Examples of a non self-immolative Spacer unit include, but are not limited to a (glycine-glycine) Spacer unit and a glycine Spacer unit (both depicted in FIG. **20** (infra). When an Exemplary Compound containing a glycine-glycine Spacer unit or a glycine Spacer unit undergoes enzymatic cleavage via a tumor-cell associated-protease, a cancer-cell-associated protease or a lymphocyte-associated protease, a glycine-glycine-Drug moiety or a glycine-Drug moiety is cleaved from L-A_a-W_w-. In one embodiment, an independent hydrolysis reaction takes place within the target cell, cleaving the glycine—Drug moiety bond and liberating the Drug.

In another embodiment, —Y— is a p-aminobenzyl alcohol (PAB) unit (see FIGS. **21** and **22**) whose phenylene portion is substituted with Q_m wherein Q is —C_1-C_8 alkyl, —O—(C_1-C_8 alkyl), -halogen, -nitro or -cyano; and m is an integer ranging from 0-4.

In one embodiment, a non self-immolative Spacer unit (—Y—) is -Gly-Gly-.

In another embodiment, a non self-immolative the Spacer unit (—Y—) is -Gly-.

In one embodiment, a Drug-Linker Compound or a Drug-Linker Ligand Conjugate is provided in which the Spacer unit is absent (y=0), or a pharmaceutically acceptable salt or solvate thereof.

Alternatively, an Exemplary Compound containing a self-immolative Spacer unit can release -D without the need for a separate hydrolysis step. In this embodiment, —Y— is a PAB group that is linked to —W_w— via the amino nitrogen atom of the PAB group, and connected directly to -D via a carbonate, carbamate or ether group. Without being bound by any particular theory or mechanism, FIG. **21** depicts a possible mechanism of Drug release of a PAB group which is attached directly to -D via a carbamate or carbonate group espoused by Toki et al. (2002) J Org. Chem. 67:1866-1872.

In FIG. **21** Q is —C_1-C_8 alkyl, —O—(C_1-C_8 alkyl), -halogen, -nitro or -cyano; m is an integer ranging from 0-4; and p ranges from 1 to about 20.

Without being bound by any particular theory or mechanism, FIG. **22** depicts a possible mechanism of Drug release of a PAB group which is attached directly to -D via an ether or amine linkage.

In FIG. **22** Q is —C_1-C_8 alkyl, —O—(C_1-C_8 alkyl), -halogen, -nitro or -cyano; m is an integer ranging from 0-4; and p ranges from 1 to about 20.

Alternatively, an Exemplary Compound containing a self-immolative Spacer unit can release -D without the need for a separate hydrolysis step. In this embodiment, —Y— is a PAB group that is linked to —W_w— via the amino nitrogen atom of the PAB group, and connected directly to -D via a carbonate, carbamate or ether group. Without being bound by any particular theory or mechanism, FIG. 21 depicts a possible mechanism of Drug release of a PAB group which is attached directly to -D via a carbamate or carbonate group espoused by Toki et al. (2002) J Org. Chem. 67:1866-1872.

'039 patent, 68:48-57.

The Specification Distinguishes Between Two Types of Spacer Units

Q. Now, do you agree that there are two kinds of spacer units that are referred to in this patent; self-immolative and non self-immolative?

A. Yes.

Q. And did you agree that a space unit can't be both self-immolative and non-self-immolative?

* * *

Q. It has to be one or the other, right?

A. Yes.

Trail Tr. at 273:19-274:5.

Exemplary Non Self-Immolative Spacers

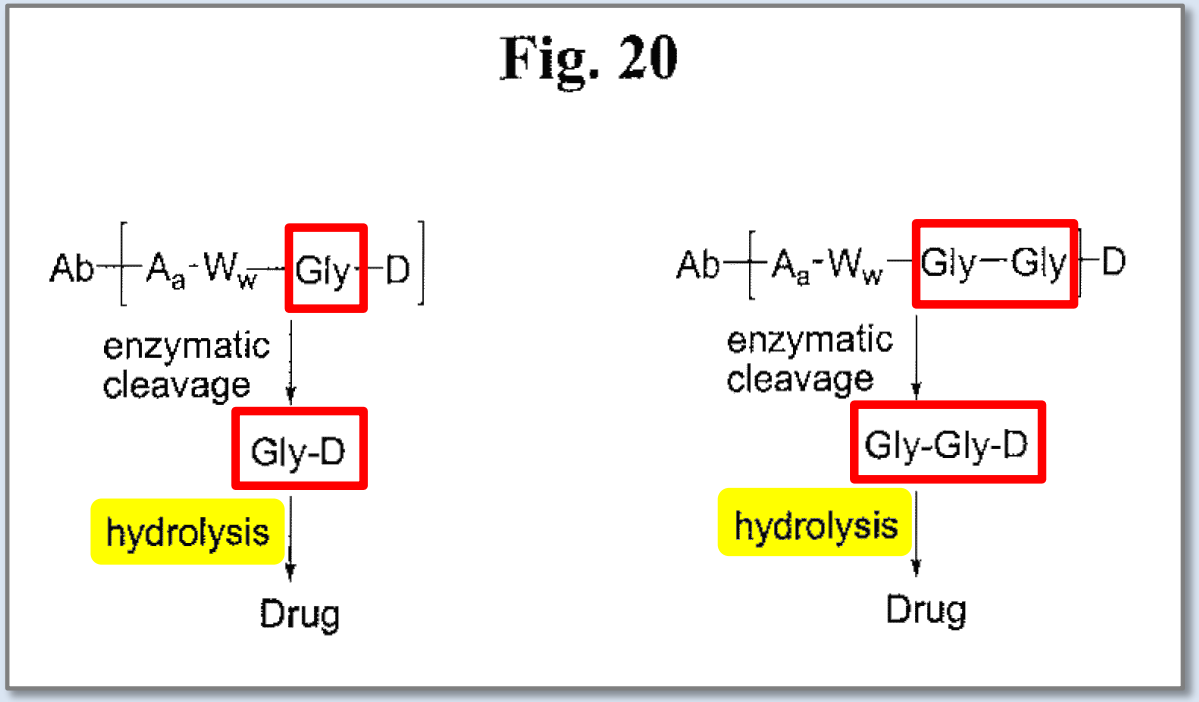
Defendants' Construction	Seagen's Construction
"wherein the drug moiety is released from Y without a separate hydrolysis step"	Plain meaning/no construction is necessary. Alternatively, "wherein Y is a spacer that degrades to release the drug after cleavage of the amino acid unit."

FIG. 20 shows examples of compounds with a **non self-immolative** Spacer unit.

'039 patent, 21:3-4.

Once inside the cell, one or more specific peptide sequences within the Linker unit are hydrolytically cleaved by one or more tumor-cell or cancer-cell-associated proteases, resulting in release of a Drug or a Drug-Linker Compound.

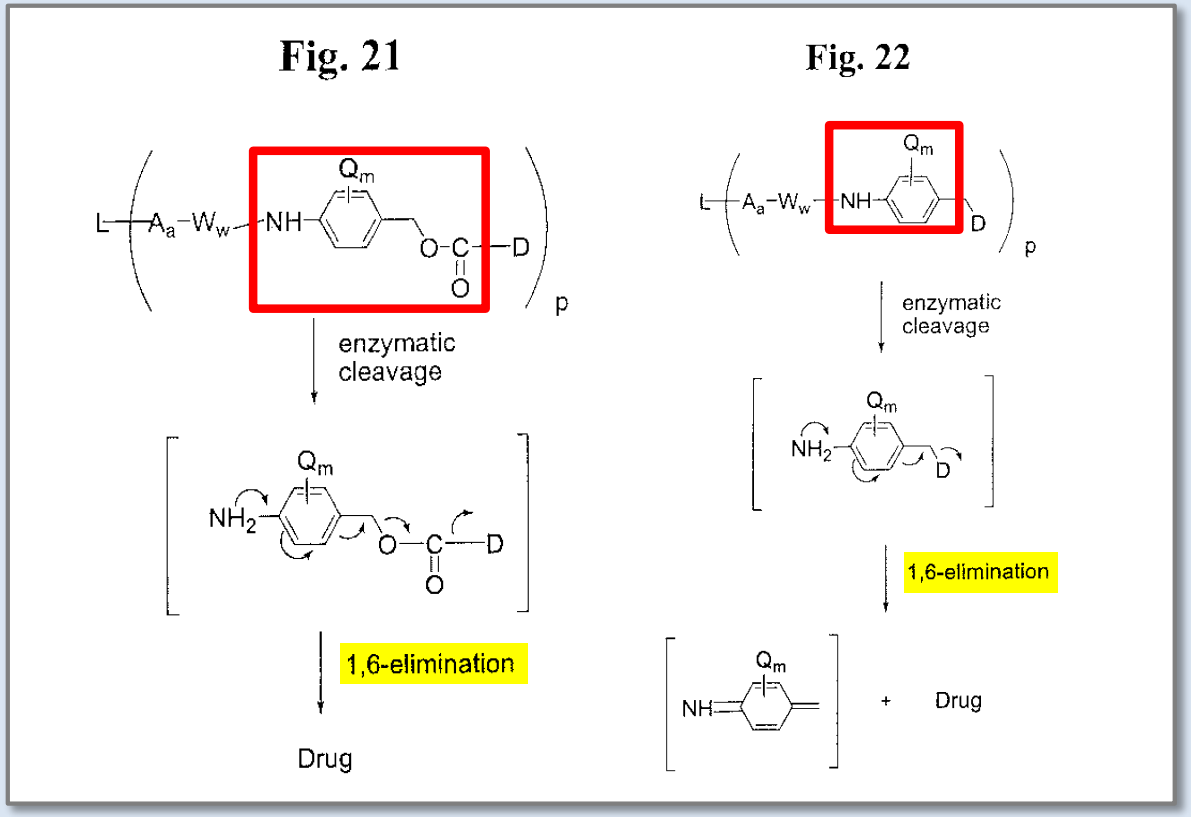
039 patent, 159:9-13.



'039 patent, 68:25-28; Figure 20.

Exemplary Self-Immolative Spacers

Defendants' Construction	Seagen's Construction
"wherein the drug moiety is released from Y without a separate hydrolysis step"	Plain meaning/no construction is necessary. Alternatively, "wherein Y is a spacer that degrades to release the drug after cleavage of the amino acid unit."



'039 patent, 68:49-67; Figures 21-22.

Seagen's Principal Argument

[T]he specification . . . provides several examples of self-immolative spacers that, contrary to DSC's construction, undergo a hydrolysis step to release the drug, demonstrating that DSC's proposed construction would impermissibly exclude such embodiments. (*Id.* (citing '039 pat. at 69:1-16).)

Seagen Reply Br. at 6-7.

Other examples of self-immolative spacers include, but are not limited to, aromatic compounds that are electronically similar to the PAB group such as 2-aminoimidazol-5-methanol derivatives (Hay et al. (1999) Bioorg. Med. Chem. Lett. 9:2237) and ortho or para-aminobenzylacetals. Spacers can be used that undergo cyclization upon amide bond hydrolysis, such as substituted and unsubstituted 4-aminobutyric acid amides (Rodrigues et al., Chemistry Biology, 1995, 2, 223), appropriately substituted bicyclo[2.2.1] and bicyclo[2.2.2] ring systems (Storm, et al., J. Amer. Chem. Soc., 1972, 94, 5815) and 2-aminophenylpropionic acid amides (Amsberry, et al., J. Org. Chem., 1990, 55, 5867). Elimination of amine-containing drugs that are substituted at the a-position of glycine (Kingsbury, et al., J. Med. Chem., 1984, 27, 1447) are also examples of self-immolative spacer useful in Exemplary Compounds.

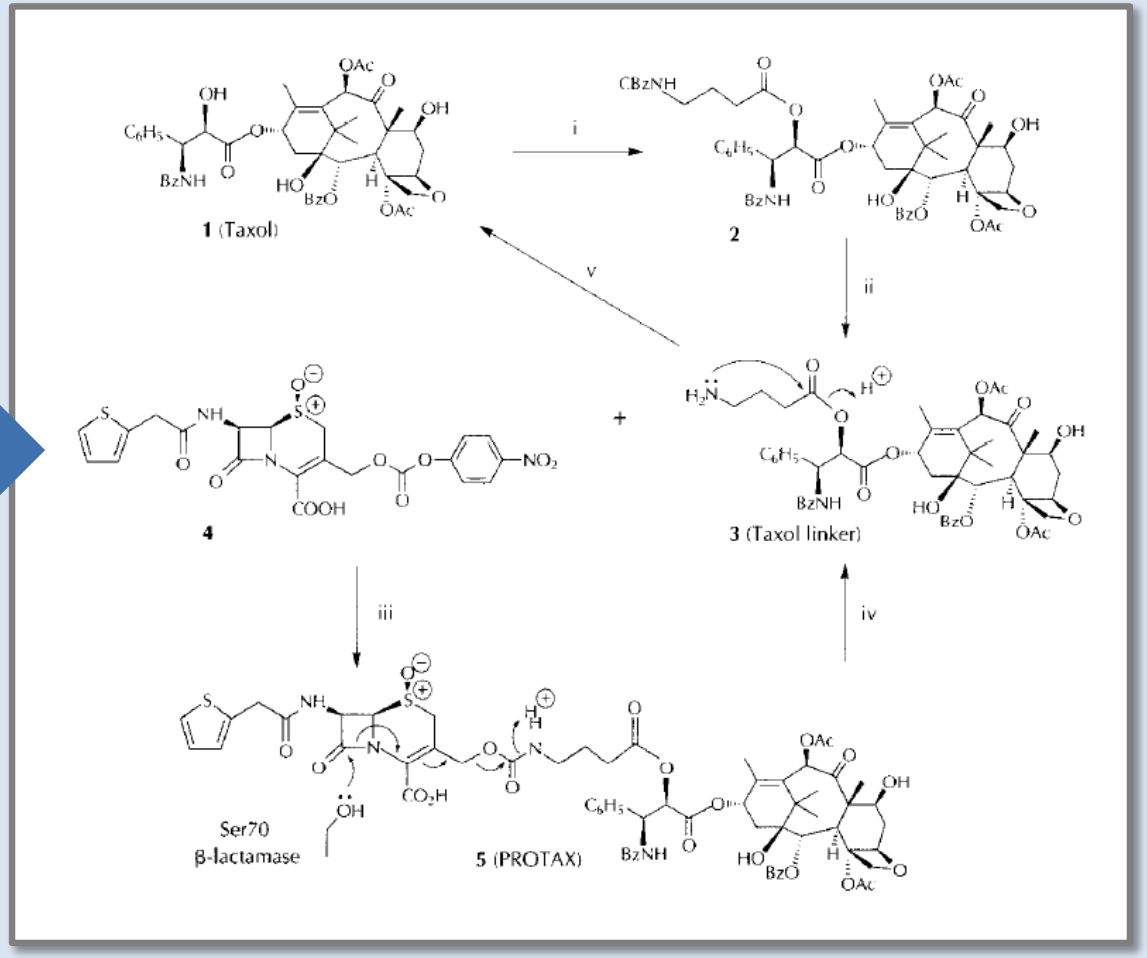
'039 patent, 69:1-16.

Response to Seagen's Argument

Other examples of self-immolative spacers include, but are not limited to, aromatic compounds that are electronically similar to the PAB group such as 2-aminoimidazol-5-methanol derivatives (Hay et al. (1999) Bioorg. Med. Chem. Lett. 9:2237) and ortho or para-aminobenzylacetals. Spacers can be used that undergo cyclization upon amide bond hydrolysis, such as substituted and unsubstituted 4-aminobutyric acid amides (Rodrigues et al., Chemistry Biology, 1995, 2, 223), appropriately substituted bicyclo[2.2.1] and bicyclo[2.2.2] ring systems (Storm, et al., J. Amer. Chem. Soc., 1972, 94, 5815) and 2-aminophenylpropionic acid amides (Amsberry, et al., J. Org. Chem., 1990, 55, 5867). Elimination of amine-containing drugs that are substituted at the a-position of glycine (Kingsbury, et al., J. Med. Chem., 1984, 27, 1447) are also examples of self-immolative spacer useful in Exemplary Compounds.

'039 patent, 69:1-16.

Showing enzymatic hydrolysis of compound **5** followed by cyclization to degrade the linker of compound **3** to yield free drug **1.**



Rodrigues 1995 at 224.

Disputed Claim Terms

Drug Moiety

Spacer Unit and Self-Immolative Spacer

Drug-Linker Issues

Intracellularly Cleaved

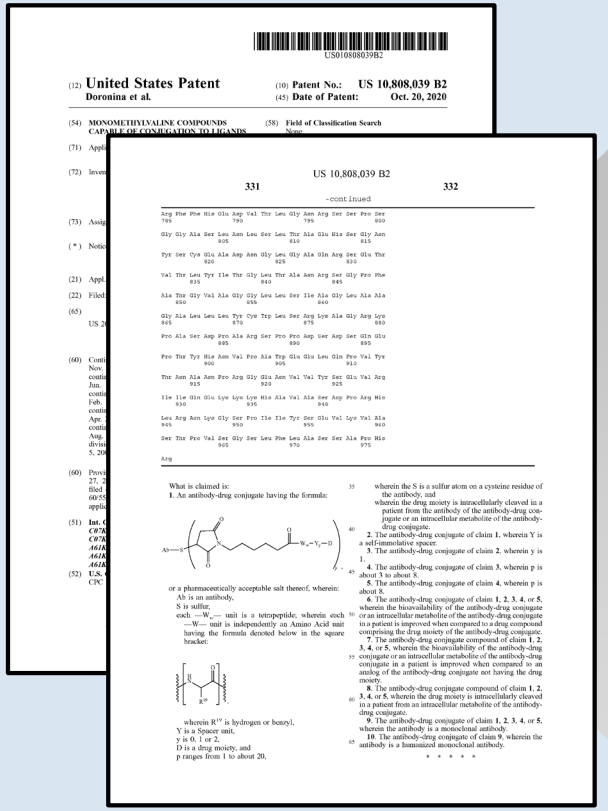
Options Presented In This *Markman* Dispute

Drug-Linker Claim Limitations:
"p ranges from 1 to about 20"

Defendants' Construction	Seagen's Construction
"p" must be an integer.	Plain meaning/no construction is necessary. A person of ordinary skill in the art would understand with reasonable certainty the scope of what is claimed. Alternatively, "The drug to antibody ratio ranges from 1 to about 20." The drug to antibody ratio, p, does not need to be an integer.

Claim Language

Claim 1 refers to “an” antibody-drug conjugate



US 10,808,039 B2

331 332

-continued

What is claimed is:

1. An antibody-drug conjugate having the formula:

or a pharmaceutically acceptable salt thereof, wherein:
Ab is an antibody,
S is sulfur,
each —W$_w$— unit is a tetrapeptide, wherein each —W— unit is independently an Amino Acid unit having the formula denoted below in the square bracket:

wherein R^{19} is hydrogen or benzyl,
Y is a Spacer unit,
y is 0, 1 or 2,
D is a drug moiety, and
p ranges from 1 to about 20,

wherein the S is a sulfur atom on a cysteine residue of the antibody, and
wherein the drug moiety is intracellularly cleaved in a patient from the antibody of the antibody-drug conjugate or an intracellular metabolite of the antibody-drug conjugate.

2. The antibody-drug conjugate of claim 1, wherein Y is a self-immolative spacer.

3. The antibody-drug conjugate of claim 2, wherein y is 1.

4. The antibody-drug conjugate of claim 3, wherein p is about 3 to about 8.

5. The antibody-drug conjugate of claim 4, wherein p is about 8.

6. The antibody-drug conjugate of claim 1, 2, 3, 4, or 5, wherein the bioavailability of the antibody-drug conjugate or an intracellular metabolite of the antibody-drug conjugate in a patient is improved when compared to a drug compound comprising the drug moiety of the antibody-drug conjugate.

7. The antibody-drug conjugate compound of claim 1, 2, 3, 4, or 5, wherein the bioavailability of the antibody-drug conjugate or an intracellular metabolite of the antibody-drug conjugate in a patient is improved when compared to an analog of the antibody-drug conjugate not having the drug moiety.

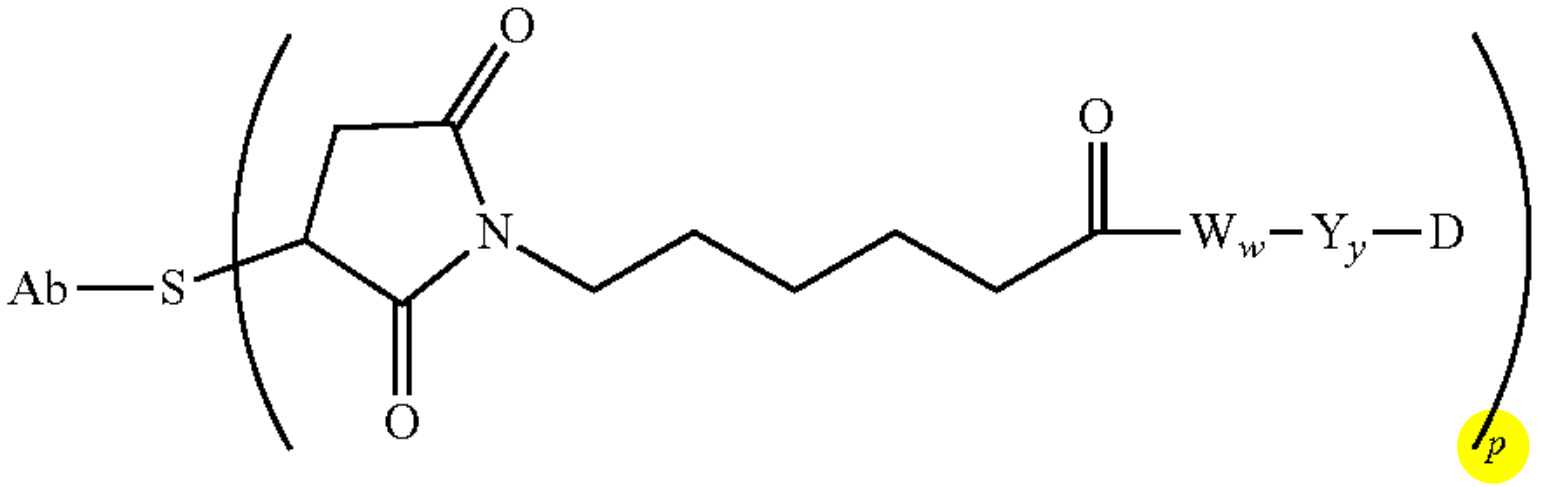
8. The antibody-drug conjugate compound of claim 1, 2, 3, 4, or 5, wherein the drug moiety is intracellularly cleaved in a patient from an intracellular metabolite of the antibody-drug conjugate.

9. The antibody-drug conjugate of claim 1, 2, 3, 4, or 5, wherein the antibody is a monoclonal antibody.

10. The antibody-drug conjugate of claim 9, wherein the antibody is a humanized monoclonal antibody.

* * * * *

1. An antibody-drug conjugate having the formula:



’039 patent, at Claim 1.

Dr. Trail's Testimony Confirms Defendants' Construction

33. I understand that DSC believes that "'p' must be an integer." As I explained above, DSC's proposed construction departs from the plain and ordinary meaning of the term. The specification describes non-integer p values. '039 patent at Figs. 7-10, 19:63-20:19, 153:19-154:12. And while an individual ADC molecule (i.e., a single antibody with one or more conjugated drug units) would have a p value that is an integer….

Trail Declaration ¶ 33.

Q. So in context of Claim 1, do you agree or disagree that P is an integer?

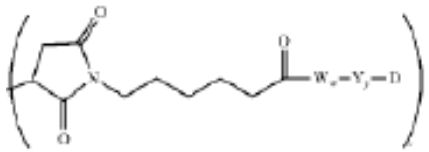
* * *

A. So it is drawn on an individual antibody basis, P would be an integer.

Trail Tr. 256:10-14.

Options Presented In This *Markman* Dispute

Drug-Linker Claim Limitations:
"wherein the S is a sulfur atom on a cysteine residue of the antibody"

Defendants' Construction	Seagen's Construction
Indefinite (the claim does not provide reasonable certainty at least regarding how the POSA would understand the scope of "a sulfur atom on a cysteine residue of the antibody" given that "p ranges from 1 to about 20") Alternatively, each of the p  are attached to a single sulfur atom.	Plain meaning/no construction is necessary. A person of ordinary skill in the art would understand with reasonable certainty the scope of what is claimed. Alternatively, "wherein S is a sulfur atom on a cysteine amino acid in the antibody."

Chef America, Inc. v. Lamb-Weston, Inc., 358 F.3d 1371 (Fed. Cir. 2004)

- "As noted, the claim requires 'heating the resulting batter-coated dough to a temperature in the range of about 400° F. to 850° F.' These are ordinary, simple English words whose meaning is clear and unquestionable. There is no indication that their use in this particular conjunction changes their meaning. They mean exactly what they say. The dough is to be heated to the specified temperature." *Id.* at 1373.

Chef America, Inc. v. Lamb-Weston, Inc., 358 F.3d 1371 (Fed. Cir. 2004)

- "The problem is that if the batter-coated dough is heated to a temperature range of 400° F. to 850° F., as the claim instructs, it would be burned to a crisp. Instead of the 'dough products suitable for freezing and finish cooking to a light, flaky, crispy texture,' . . . which the patented process is intended to provide, the resultant product of such heating will be something that, in the words of one of the attorneys in this case, resembles a charcoal briquet." *Id.* at 1373.

Chef America, Inc. v. Lamb-Weston, Inc., 358 F.3d 1371 (Fed. Cir. 2004)

- "This court, however, repeatedly and consistently has recognized that courts may not redraft claims, whether to make them operable or to sustain their validity. *See, e.g.*, *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1349 (Fed.Cir.2002); … *Process Control Corp. v. Hydreclaim Corp*., 190 F.3d 1350, 1357 (Fed.Cir.1999)." *Id.* at 1374.
- "Even 'a nonsensical result does not require the court to redraft the claims of the ['290] patent. Rather, where as here, claims are susceptible to only one reasonable interpretation and that interpretation results in a nonsensical construction of the claim as a whole, the claim must be invalidated.'" *Id.*
- "Thus, in accord with our settled practice we construe the claim as written, not as the patentees wish they had written it. As written, the claim unambiguously requires that the dough be heated to a temperature range of 400° F. to 850° F." *Id.*

Parentheses Placement Matters

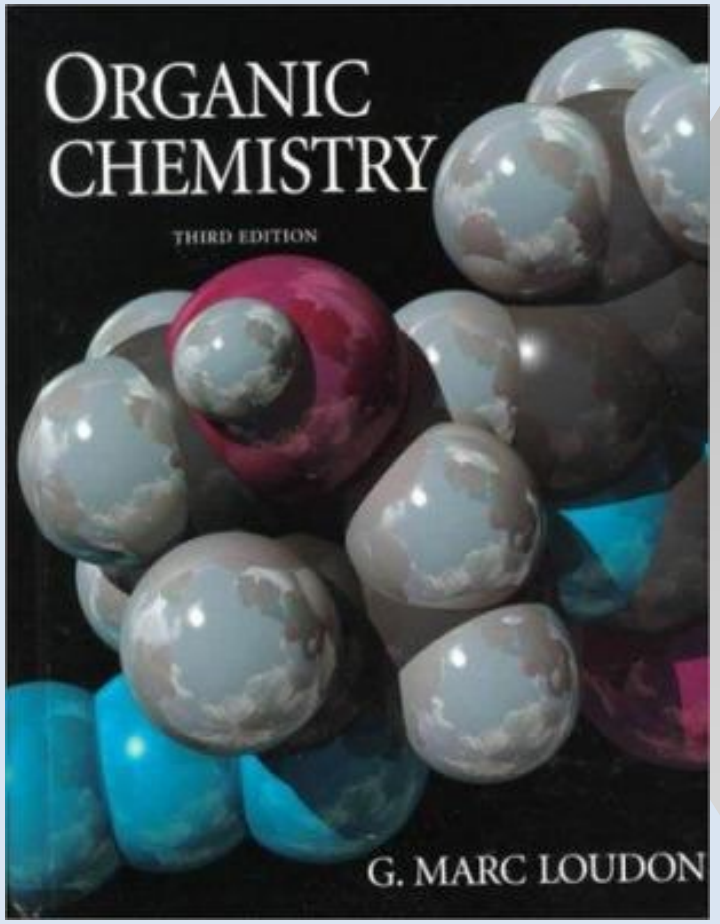


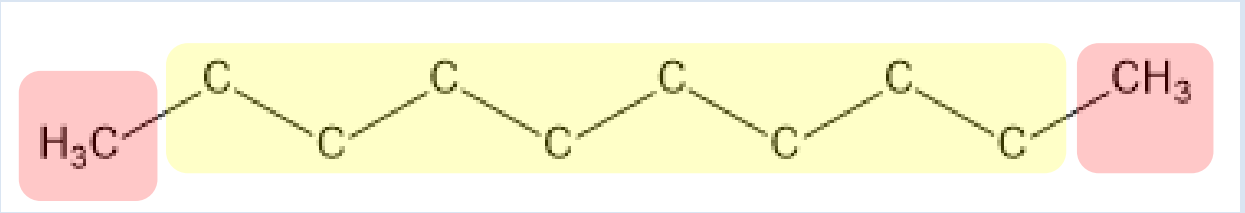
Table 2.2 Nomenclature of Some Short Branched-Chain Alkyl Groups

Group structure	*Condensed structure*	*Written name*	*Pronounced name*
$CH_3CH(CH_3)-$	$(CH_3)_2CH-$	isopropyl	isopropyl
$CH_3CH(CH_3)CH_2-$	$(CH_3)_2CHCH_2-$	isobutyl	isobutyl
$CH_3CH_2CH(CH_3)-$	—	*sec*-butyl	secondary butyl
$CH_3C(CH_3)_2-$	$(CH_3)_3C-$	*tert*-butyl (or *t*-butyl)	tertiary butyl
$CH_3C(CH_3)_2CH_2-$	$(CH_3)_3CCH_2-$	neopentyl	neopentyl

Organic Chemistry, Third Edition, G. Marc. Loudon, 1988, p. 58.

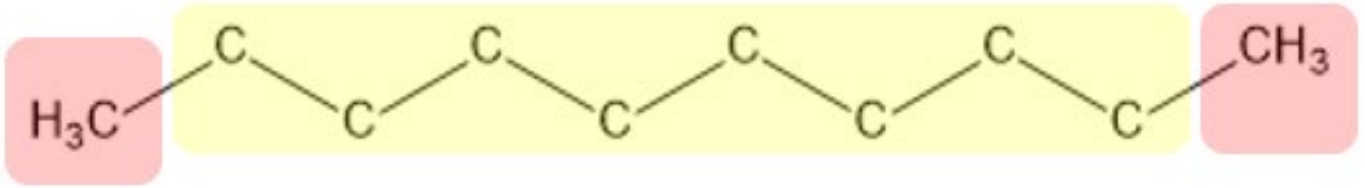
Scripps Research Institute v. Illumina, Inc., 782 F. App'x 1018 (Fed. Cir. 2019)

- "[T]he formula $CH_3(CH_2)_8CH_3$ represents the straight-chain hydrocarbon decane. The subscript outside the parentheses indicates how many times the group inside the parentheses repeats, *i.e.*, that there are eight saturated carbons singly bonded to one another in between two methyl groups." *Id.* at 1023.
- This is "ordinary chemical nomenclature." *Id.*

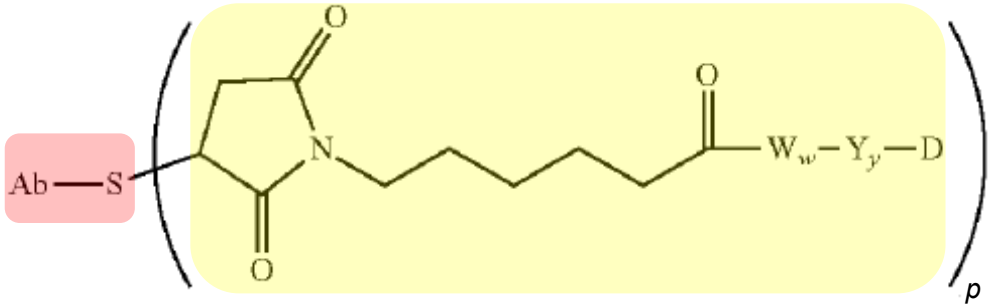


Applying Chemical Nomenclature to Patent's Structures

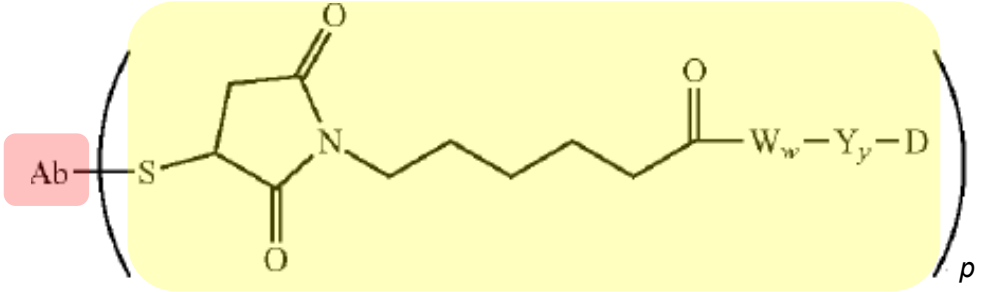
Scripps example: $CH_3(CH_2)_8CH_3$



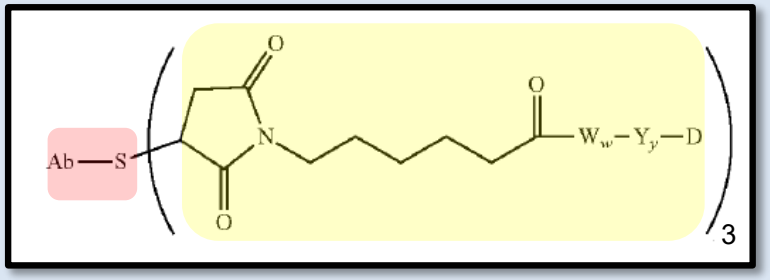
'039 patent, Claim 1



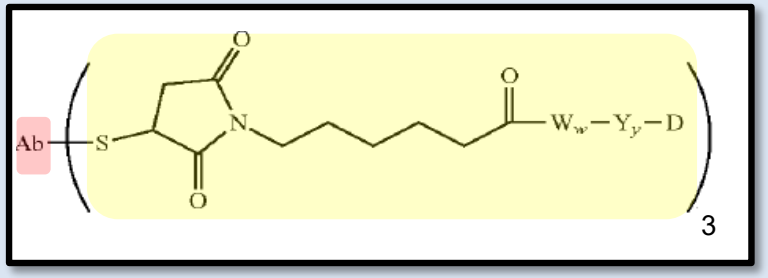
'039 patent, 70:23-27



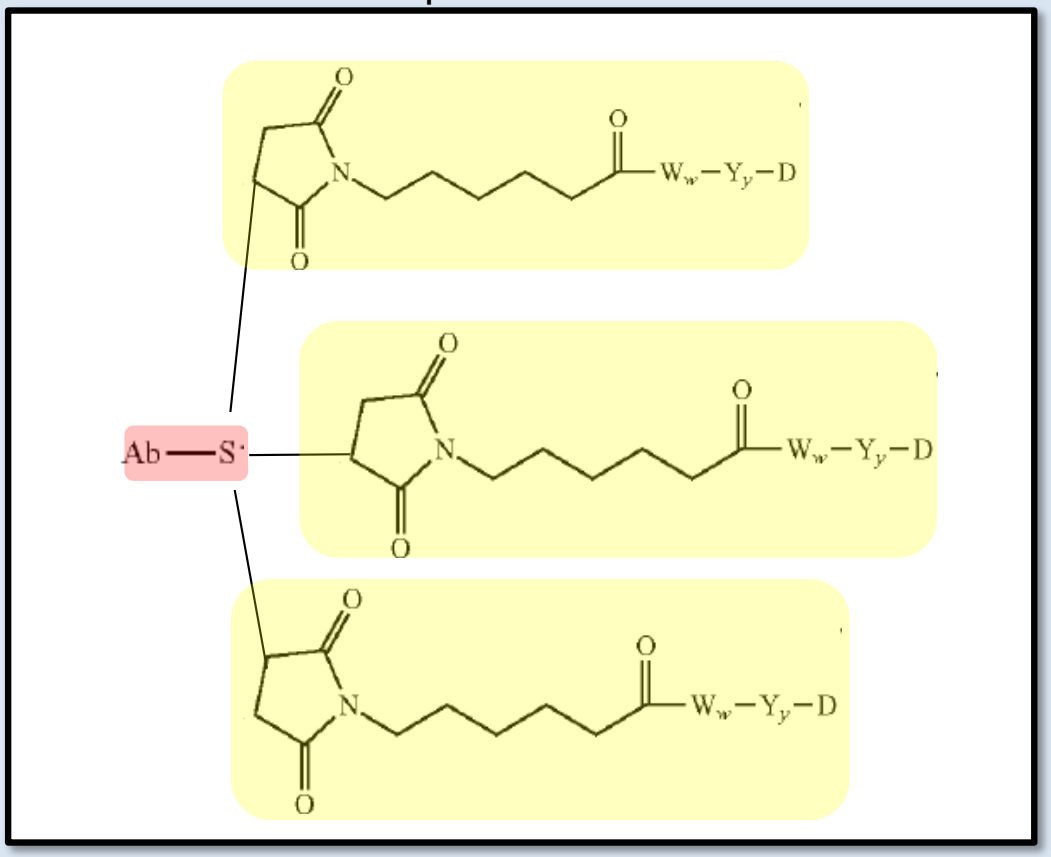
Applying Chemical Nomenclature to Patent's Structures Where p = 3

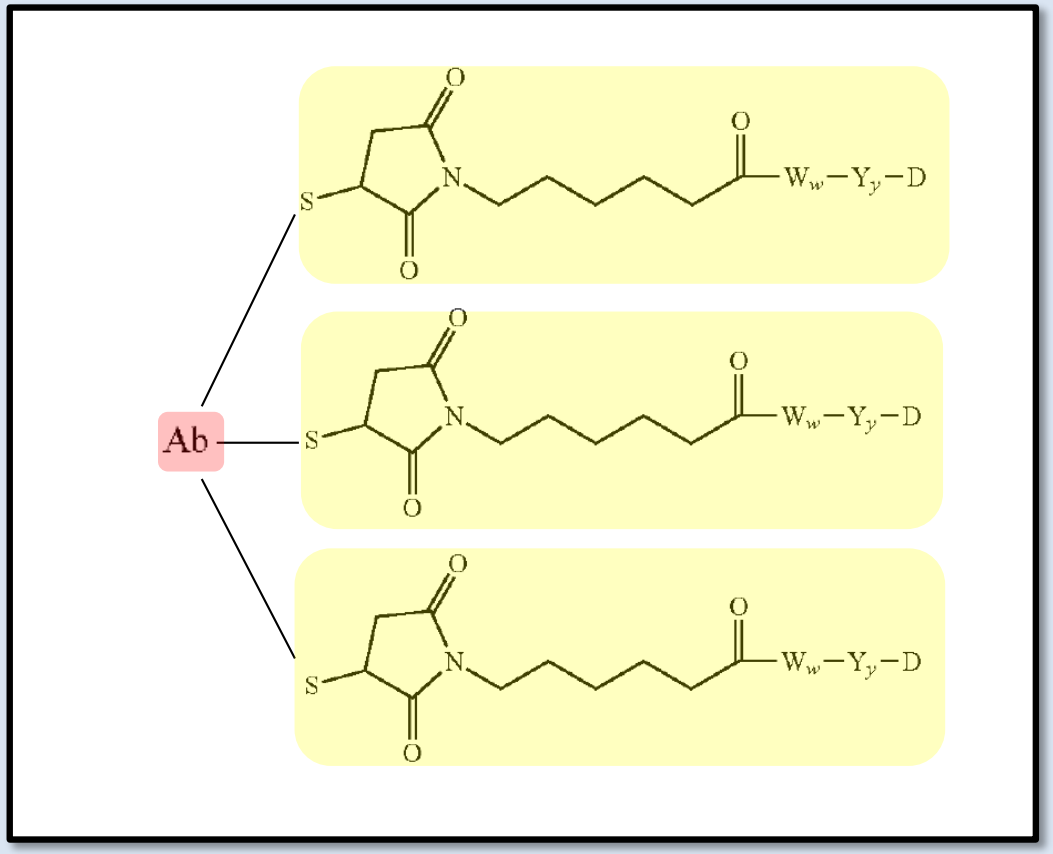


'039 patent Claim 1.

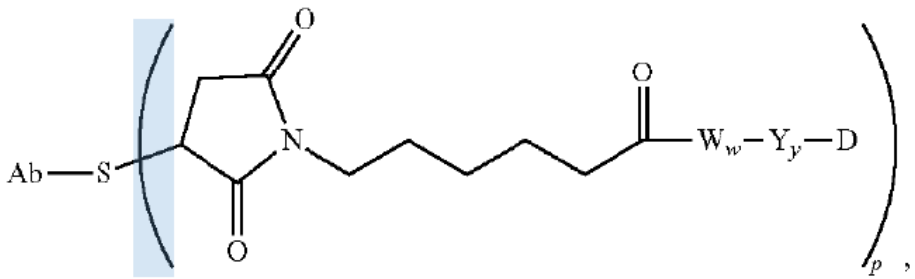


'039 patent 70:23-27.

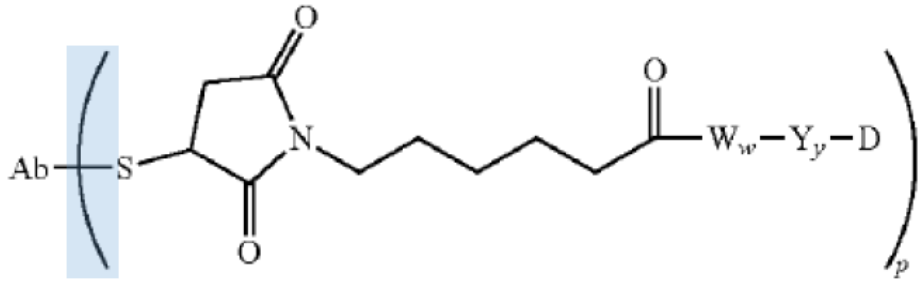




The Claim v. The Specification



('039 patent, Claim 1)



('039 patent, 70:23-27)

Dr. Trail conceded these are not the same structures

Q. Does that mean you think the drawings are the same?
A. I think what they accomplish is intended to be the same.
Q. But that's not my question. My question is: Do you agree that the two drawings are not the same?

* * *

A. The drawings depicted here are not the same.

Trail Tr. 264:1-10.

Chef America, Inc. v. Lamb-Weston, Inc., 358 F.3d 1371 (Fed. Cir. 2004)

- The patentees "argue only that 'to' should be construed to mean 'at' because **otherwise the patented process could not perform the function the patentees intended**. As we have noted, however, **we have repeatedly declined to rewrite unambiguous patent claim language for that reason**."

Q. Okay. And would you agree that from the standpoint of, of conveying mild clues in terms of structure, that it requires precision?

* * *

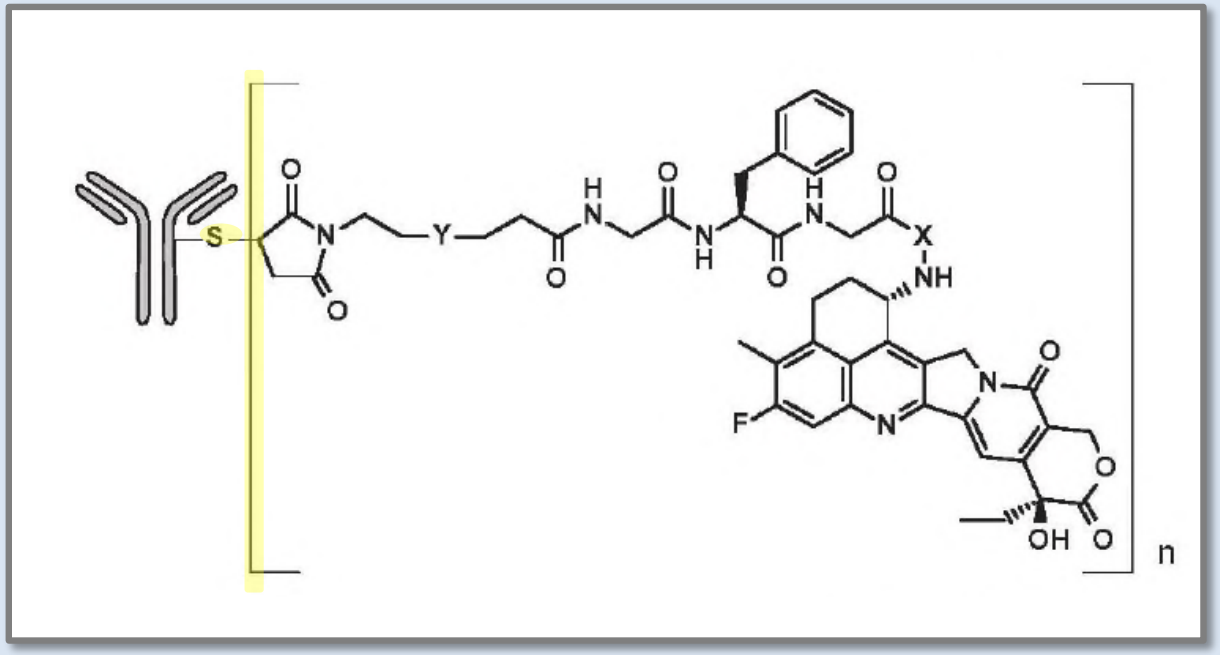
A. So I have seen this drawing in this both fashions in this patent. I've seen it drawn in both fashions in Daiichi publications. In looking at the structures, it's clear to me that the intention is to look at the linkers attached to a cysteine, so the sulfur in a cystine with a numeric being one linker per sulfur.

Trail Tr. 264:1-10, 265:8-20.

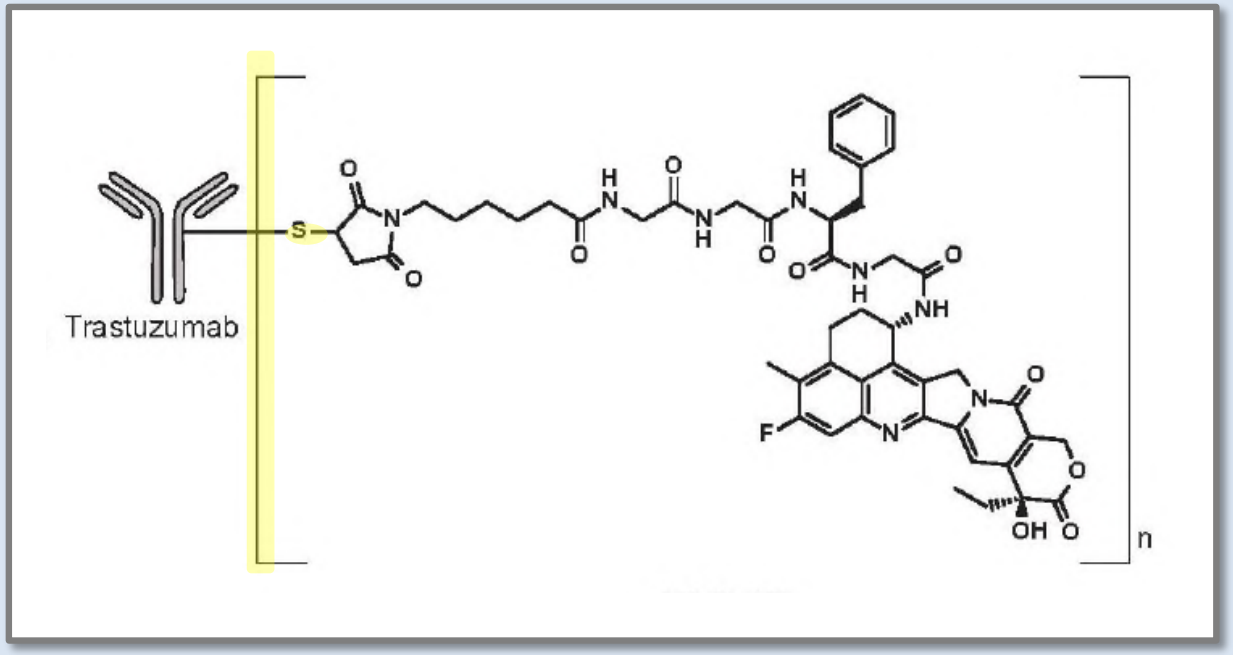
Nakada et al. 2016

For example, the article by Nakada et al.—a publication by DSC scientists—provides a similar diagram to that found in Claim 1's formula, where a sulfur atom (S) appears outside the parentheses that illustrate the drug-linker unit. (Ex. 18 at SGIEDTX00008241.) Thus, DSC's own scientists have found that this is a clear and definite way to notate an ADC that has the structure of Claim 1. [No citation.]

Seagen Reply Br. at 9.



Ex. 18 to Seagen Opening Br.

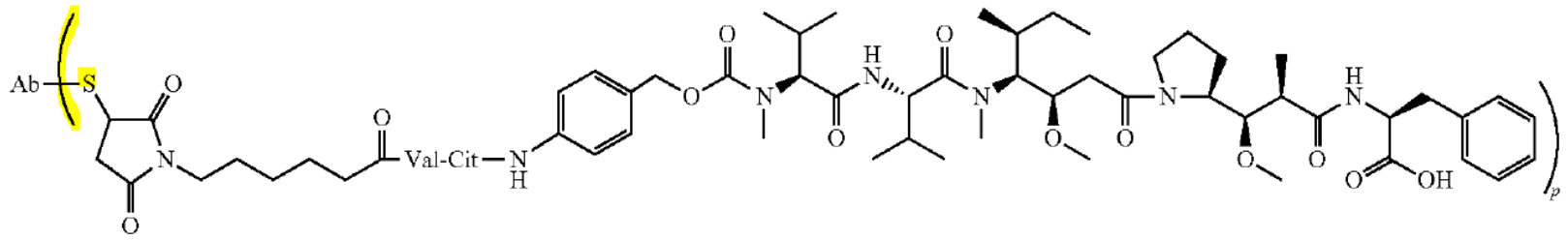


Ex. 18 to Seagen Opening Br.

Other Seagen Patents in Same Family

US Patent No. 8,703,714

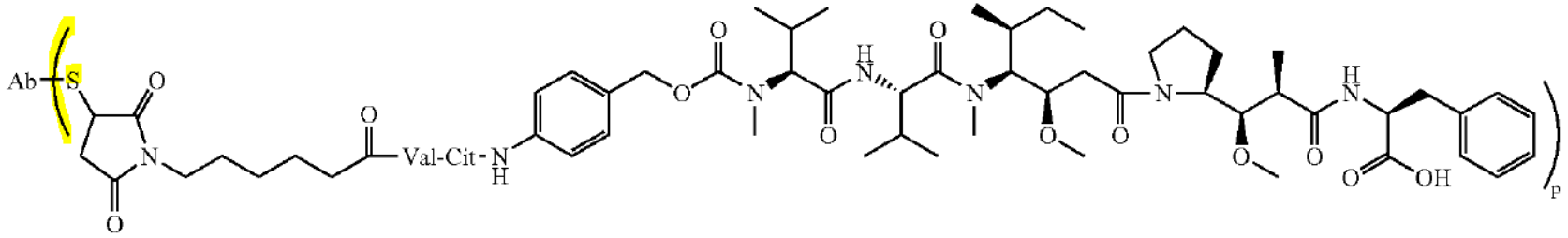
35. The antibody-drug conjugate of claim **1**, having the formula:



Ab-MC-vc-PAB-MMAF

US Patent No. 7,994,135

23. An antibody-drug conjugate compound of claim **1** having the formula:



Ab-MC-vc-PAB-MMAF

Indefiniteness

- *Synchronoss Techs., Inc. v. Dropbox, Inc.*, 987 F.3d 1358, 1366–67 (Fed. Cir. 2021) ("Here, the asserted claims of the '446 patent are nonsensical and require an impossibility . . . . We therefore hold that the claims are indefinite as a matter of law under § 112, paragraph 2.")
- *Invensys Sys., Inc. v. Emerson Elec. Co.*, No. 12-799, 2014 WL 3976371, at *5 (E.D. Tex. Aug. 6, 2014) ("Because the plain language of all three independent claims of the '131 Patent require performing a calculation that is mathematically impossible, the claims are indefinite and render the '131 Patent invalid.")

In contrast, DSC would have the Court insert limitations into the term so that every drug-linker unit, "p," must bond with a "*single* sulfur atom." This construction would mean that, in Claim 5, all "about 8" drug-linker units would have to be bonded to the same sulfur atom. As sulfur can only support six bonds maximum (as opposed to "about 8"), the construction would result in a scientific impossibility that DSC asserts renders the claim indefinite. Yet DSC presents no evidence that this is how one of ordinary skill would interpret the claims, and the inoperability of its own construction confirms skilled artisans, in fact, would not interpret them as DSC proposes. (*See* Trail Decl. ¶ 40.) The Court should reject DSC's attempt to create indefiniteness where there is none. If helpful for lay jurors, however, the scientific term "residue" could be construed as "amino acid."

Seagen Opening Br. at 15.

Disputed Claim Terms

Drug Moiety

Spacer Unit and Self-Immolative Spacer

Drug-Linker Issues

Intracellularly Cleaved

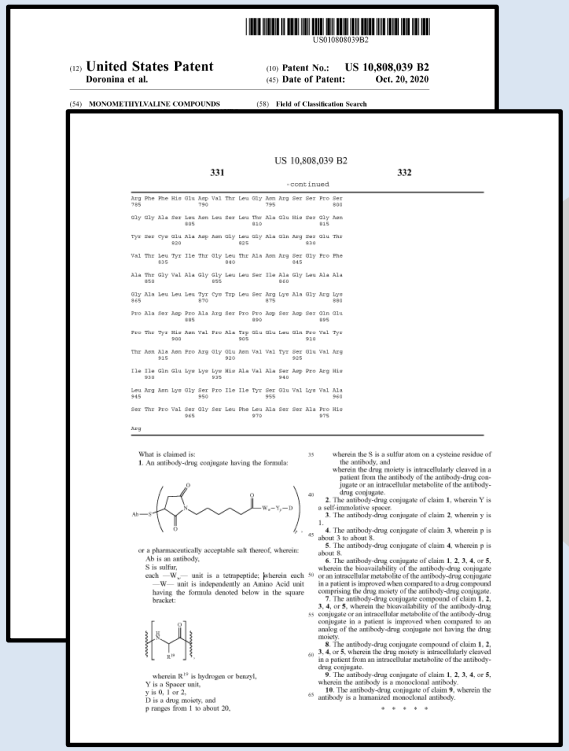
Options Presented in This *Markman* Dispute

Intracellular Cleavage: "wherein the drug moiety is intracellularly cleaved in a patient from the antibody of the antibody-drug conjugate or an intracellular metabolite of the antibody-drug conjugate"

Defendants' Construction	Seagen's Construction
"wherein the free drug moiety dissociates from the antibody as a result of a metabolic process or reaction inside a cell in a patient that breaks the covalent attachment, of an antibody-drug conjugate or an intracellular metabolite of an antibody-drug conjugate, between the drug moiety (D) and the antibody (Ab)" *See, e.g.*, '039 patent, 29:48-57.	Plain meaning/no construction is necessary. Alternatively, "wherein the drug is separated within a cell from the antibody of the antibody-drug conjugate or a metabolite of the antibody-drug conjugate."

Disputed Claim Term

- The claims expressly require that "***the drug moiety*** is intracellularly cleaved"



US10808039B2

(12) **United States Patent**
Doronina et al.

(10) **Patent No.: US 10,808,039 B2**
(45) **Date of Patent: Oct. 20, 2020**

(54) MONOMETHYLVALINE COMPOUNDS (58) Field of Classification Search

US 10,808,039 B2

331 332

-continued

What is claimed is:

1. An antibody-drug conjugate having the formula:

or a pharmaceutically acceptable salt thereof, wherein:
Ab is an antibody,
S is sulfur,
each —W_w— unit is a tetrapeptide; wherein each —W— unit is independently an Amino Acid unit having the formula denoted below in the square bracket:

wherein R^{17} is hydrogen or benzyl,
Y is a Spacer unit,
y is 0, 1 or 2,
D is a drug moiety, and
p ranges from 1 to about 20.

wherein the S is a sulfur atom on a cysteine residue of the antibody, and
wherein the drug moiety is intracellularly cleaved in a patient from the antibody of the antibody-drug conjugate or an intracellular metabolite of the antibody-drug conjugate.

2. The antibody-drug conjugate of claim **1**, wherein Y is a self-immolative spacer.

3. The antibody-drug conjugate of claim **2**, wherein y is 1.

4. The antibody-drug conjugate of claim **3**, wherein p is about 3 to about 8.

5. The antibody-drug conjugate of claim **4**, wherein p is about 8.

6. The antibody-drug conjugate of claim **1**, **2**, **3**, **4**, or **5**, wherein the bioavailability of the antibody-drug conjugate or an intracellular metabolite of the antibody-drug conjugate in a patient is improved when compared to a drug compound comprising the drug moiety of the antibody-drug conjugate.

7. The antibody-drug conjugate compound of claim **1**, **2**, **3**, **4**, or **5**, wherein the bioavailability of the antibody-drug conjugate or an intracellular metabolite of the antibody-drug conjugate in a patient is improved when compared to an analog of the antibody-drug conjugate not having the drug moiety.

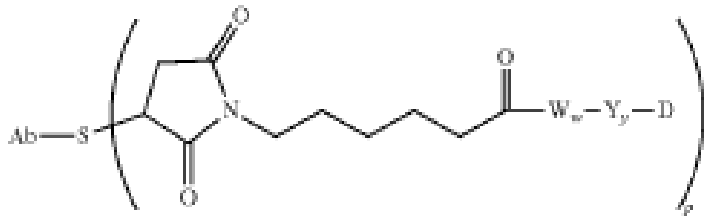
8. The antibody-drug conjugate compound of claim **1**, **2**, **3**, **4**, or **5**, wherein the drug moiety is intracellularly cleaved in a patient from an intracellular metabolite of the antibody-drug conjugate.

9. The antibody-drug conjugate of claim **1**, **2**, **3**, **4**, or **5**, wherein the antibody is a monoclonal antibody.

10. The antibody-drug conjugate of claim **9**, wherein the antibody is a humanized monoclonal antibody.

* * * * *

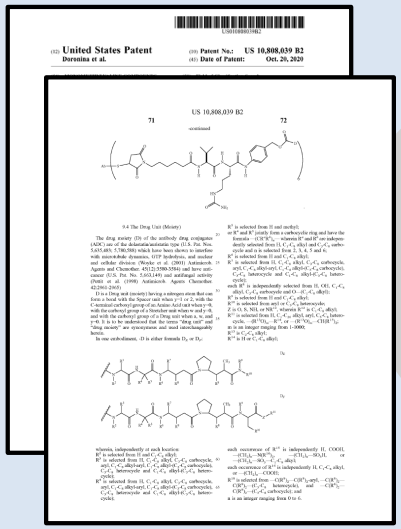
1. An antibody-drug conjugate having the formula:



. . . wherein . . . D is a drug moiety . . .
. . . wherein the drug moiety is intracellularly cleaved in a patient from the antibody of the antibody-drug conjugate or an intracellular metabolite of the antibody-drug conjugate.

See, e.g., '039 patent, Claim 1.

Patentee Used Lexicography to Define "Intracellularly Cleaved"



The terms "intracellularly cleaved" and "intracellular cleavage" refer to a metabolic process or reaction inside a cell on an [sic] Drug-Ligand Conjugate, a Drug-Linker-Ligand Conjugate, an antibody drug conjugate (ADC) or the like whereby the covalent attachment, e.g., the linker, between the drug moiety (D) and the antibody (Ab) is broken, resulting in the free drug dissociated from the antibody inside the cell.

- The Patentee's definition has four requirements:
  1. a specific process ("a metabolic process or reaction");
  2. the location in which the process occurs ("inside a cell");
  3. what must be "broken" ("the covalent attachment . . . between the drug moiety (D) and the antibody (Ab)"); and
  4. the result ("the ***free*** drug dissociated from the antibody inside the cell")

See, e.g., '039 patent, 29:48-57.

Defendants' Construction Applies Patentee's Lexicography to the Claim Limitation

Claim Limitation	Defendants' Construction
". . . wherein the drug moiety is **intracellularly cleaved** in a patient from the antibody of the antibody-drug conjugate or an intracellular metabolite of the antibody-drug conjugate"	wherein the free drug moiety dissociates from the antibody as a result of a metabolic process or reaction inside a cell in a patient that breaks the covalent attachment, of an antibody-drug conjugate or an intracellular metabolite of an antibody-drug conjugate, between the drug moiety (D) and the antibody (Ab)

Lexicography from 29:48-57:

The terms "intracellularly cleaved" and "intracellular cleavage" refer to a metabolic process or reaction inside a cell on an Drug-Ligand Conjugate, a Drug-Linker-Ligand Conjugate, an antibody drug conjugate (ADC) or the like whereby the covalent attachment, e.g., the linker, between the drug moiety (D) and the antibody (Ab) is broken, resulting in the free drug dissociated from the antibody inside the cell.

See, e.g., '039 patent, 29:48-57, Claim 1.

Defendants' Construction Applies Patentee's Lexicography to the Claim Limitation

Claim Limitation	Defendants' Construction
". . . wherein the drug moiety is **intracellularly cleaved** in a patient from the antibody of the antibody-drug conjugate or an intracellular metabolite of the antibody-drug conjugate"	wherein the free drug moiety dissociates from the antibody as a result of a metabolic process or reaction inside a cell in a patient that breaks the covalent attachment, of an antibody-drug conjugate or an intracellular metabolite of an antibody-drug conjugate, between the drug moiety (D) and the antibody (Ab)

Lexicography from 29:48-57:

The terms "intracellularly cleaved" and "intracellular cleavage" refer to a metabolic process or reaction inside a cell on an [sic] Drug-Ligand Conjugate, a Drug-Linker-Ligand Conjugate, an antibody drug conjugate (ADC) or the like whereby the covalent attachment, e.g., the linker, between the drug moiety (D) and the antibody (Ab) is broken, resulting in the free drug dissociated from the antibody inside the cell.

See, e.g., '039 patent, 29:48-57, Claim 1.

Seagen Attempts to Avoid the Definition's "Free Drug" Requirement

- Under the guise of "avoid[ing] jury confusion," Seagen omits the specification's explicit requirement that intracellular cleavage "result[s] in the ***free*** drug dissociat[ing] from the antibody"

See Seagen Reply Br. at 10.

- **Seagen**, however, states that it would not oppose referencing the "free drug" requirement, **but only if "free drug" is regarded as referring to "the active drug component of an ADC."**

See id.

- But the claim **requires** that the "drug moiety" be intracellularly cleaved

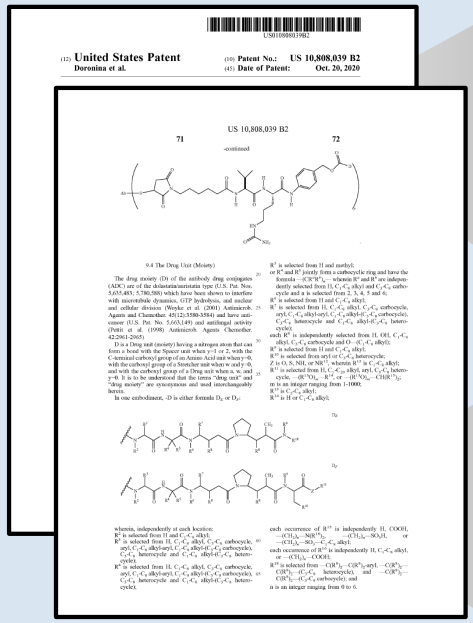
See '039 patent, Claim 1.

"Covalent Attachment" Includes the Linker

- Seagen argues that Defendants changed the meaning by not including the Patentee's stated example of the "covalent attachment" requirement

See Seagen Opening Br. at 20.

- Adding "e.g., the linker" to Defendants' proposed construction would be fine



(12) United States Patent
Doronina et al.

(10) Patent No.: US 10,808,039 B2
(45) Date of Patent: Oct. 20, 2020

US 10,808,039 B2

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-continued

9.4 The Drug Unit (Moiety)

The drug moiety (D) of the antibody drug conjugates (ADC) are of the dolastatin/auristatin type (U.S. Pat. Nos. 5,635,483; 5,780,588) which have been shown to interfere with microtubule dynamics, GTP hydrolysis, and nuclear and cellular division (Woyke et al. (2001) Antimicrob. Agents and Chemother. 45(12):3580-3584) and have anti-cancer (U.S. Pat. No. 5,663,149) and antifungal activity (Pettit et al. (1998) Antimicrob. Agents Chemother. 42:2961-2965).

It is a Drug unit (moiety) having a nitrogen atom that can form a bond with the Spacer unit when y=1 or 2, with the C-terminal carboxyl group of an Amino Acid unit when y=0, with the carbonyl group of a Stretcher unit when w and y=0, and with the carbonyl group of a Drug unit when n, w, and y=0. It is to be understood that the terms "drug unit" and "drug moiety" are synonymous and used interchangeably herein.

In one embodiment, -D is either formula D_E or D_F:

wherein, independently at each location:

R^2 is selected from H and C_1-C_8 alkyl;

R^3 is selected from H, C_1-C_8 alkyl, C_3-C_8 carbocycle, C_1-C_8 alkoxy, C_1-C_8 alkyl-C_1-C_8 alkoxy, C_6-C_{10} aryl, C_1-C_8 alkyl-(C_6-C_{10} aryl), C_6-C_{10} aryl-C_1-C_8 alkyl, C_3-C_8 heterocycle and C_1-C_8 alkyl-(C_3-C_8 heterocycle);

R^4 is selected from H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle and C_1-C_8 alkyl-(C_3-C_8 heterocycle);

R^5 is selected from H and methyl;

or R^4 and R^5 jointly form a carbocyclic ring and have the formula $-(CR^{a}R^{b})_n-$ wherein R^a and R^b are independently selected from H, C_1-C_8 alkyl and C_3-C_8 carbocycle and n is selected from 2, 3, 4, 5 and 6;

R^6 is selected from H and C_1-C_8 alkyl;

R^7 is selected from H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle and C_1-C_8 alkyl-(C_3-C_8 heterocycle);

each R^8 is independently selected from H, OH, C_1-C_8 alkyl, C_3-C_8 carbocycle and O-(C_1-C_8 alkyl);

R^9 is selected from H and C_1-C_8 alkyl;

R^{10} is selected from aryl or C_3-C_8 heterocycle;

Z is O, S, NH, or NR^{12}, wherein R^{12} is C_1-C_8 alkyl;

R^{11} is selected from H, C_1-C_{20} alkyl, aryl, C_3-C_8 heterocycle, $-(R^{13}O)_m-R^{14}$, or $-(R^{13}O)_m-CH(R^{15})_2$;

m is an integer ranging from 1-1000;

R^{13} is C_2-C_8 alkyl;

R^{14} is H or C_1-C_8 alkyl;

each occurrence of R^{15} is independently H, COOH, $-(CH_2)_n-N(R^{16})_2$, $-(CH_2)_n-SO_3H$, or $-(CH_2)_n-SO_3-C_1$-C_8 alkyl;

each occurrence of R^{16} is independently H, C_1-C_8 alkyl, or $-(CH_2)_n-COOH$;

R^{17} is selected from $-(CR^{a}_2)_n-C(R^{a})_2$-aryl-$-C(R^{a})_2-C(R^{a})_2-(C_3$-$C_8$ heterocycle), and $-C(R^{a})_2-C(R^{a})_2-(C_3$-$C_8$ carbocycle); and

n is an integer ranging from 0 to 6.

The terms "intracellularly cleaved" and "intracellular cleavage" refer to a metabolic process or reaction inside a cell on an [sic] Drug-Ligand Conjugate, a Drug-Linker-Ligand Conjugate, an antibody drug conjugate (ADC) or the like whereby the covalent attachment, e.g., the linker, between the drug moiety (D) and the antibody (Ab) is broken, resulting in the free drug dissociated from the antibody inside the cell.

Defendants' Proposed Construction: "wherein the free drug moiety dissociates from the antibody as a result of a metabolic process or reaction inside a cell in a patient that breaks the covalent attachment, of an antibody-drug conjugate or an intracellular metabolite of an antibody-drug conjugate, between the drug moiety (D) and the antibody (Ab)"

See, e.g., '039 patent, 29:48-57, Claim 1.